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YOUTH VIOLENCE AND THE BRAIN: EXPOSURE TO VIOLENCE AND DEACTIVATION OF AN INSULAR-FRONTAL NETWORK OF CORTICAL AREAS ASSOCIATED WITH INHIBITORY CONTROL

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Pontifícia Universidade Católica
do Rio Grande do Sul

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Dissertação apresentada como requisito para a obtenção do grau de Mestre pelo Programa de Pós-Graduação em Medicina e Ciências da Saúde – Neurociências da Pontifícia Universidade Católica do Rio Grande do Sul.

Orientador: Dr. Augusto Buchweitz

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It all started in 2013, when the Brain Institute was under construction and my class from Medical School visited the installations. The fMRI team was testing the parameters, and as we watched the process I thought to myself, I need to be part of this!

Even though this work is part of a larger project (Projeto VIVA) and I'm presenting a fragment of the findings that we have so far, this work symbolizes my journey to and through the realm of research and neuroscience. I could not have done this without the help, guidance and support from many amazing people on the way. First of all, thanks to my mentor Augusto Buchweitz for believing in me since the beginning, for giving me the opportunity and pulling me and pushing me all these years. It's an honor to be part of your team. Alexandre Franco, you were there too and shone your light of wisdom and sagacity on many crucial parts of this journey. Mirna Wetters Portuguez and Jaderson Costa da Costa, you made this all possible in so many ways, thank you for everything. Nathalia Bianchini Esper, my friend and fMRI guru; all researchers and students who were involved in the Projeto VIVA; and the amazing staff from all departments at the Brain Institute, thank you for being part of this.

My deepest thanks to the Inter-American Development Bank, for believing in the project and sponsoring the research and my scholarship. Thank you Pontifícia Universidade Católica do Rio Grande do Sul for being my home and the fertile ground for my achievements for all these years.

ABSTRACT

This study investigates the effects of preadolescent exposure to violence on brain function using functional magnetic resonance imaging (fMRI) and a task that tests executive functions. Executive functions are impaired in different disorders, and also as a result of adverse life conditions such as stress and abuse. Based on the literature, we hypothesized that exposure to violence would impact executive functions and their neurobiological correlates. The task performed during fMRI was a sustainned attetion task that tests for inhibitory control. Exposure to violence and behavior were investigated using self-reports (Juvenile Victimization Questionnaire and the Childhood Behavior Checklist). In total, 42 preadolescents (ages 10-14), recruited from public schools in one of the most violent cities in the world participated in the study. Results showed a significant negative correlation between the scores for exposure to violence and brain funtion in a fronto-parietal-insular network: preadolescents with higher levels of exposure to violence showed deactivation of bilateral insula and superior frontal cortex. These brain areas are associated with attention and inhibitory control. The findings provide evidence that preadolescent victimization and exposure to violence alters the neural patterns underlying executive functioning, and suggest that executive function tranining may be a candidate for targeted interventions in preadolescents exposed to violence.

Key words: Neuroimaging. Functional Magnetic Resonance. fMRI. Violence. Preadolescents. Executive Functions. Inhibitory Control. Insula. Change Task. Juvenile Victimization Questionnaire (JVQ). Child Behavior Checklist (CBCL).

RESUMO

O objetivo deste estudo foi investigar os efeitos causados pela exposição crônica à violência em pré-adolescentes, utilizando-se de Ressonância Magnética Funcional (fMRI) e uma tarefa que testa funções executivas. Estudos sugerem que funções executivas podem se afetadas por diferentes enfermidades, como resultado de condições de vida desfavoráveis e exposição ao estresse e abuso. Com base na literatura, o presente estudo parte da hipótese de que exposição crônica à violência está associada com efeitos nas funções executivas e seus correlatos neurobiológicos. Realizou-se uma tarefa de atenção contínua que testa controle inibitório. Exposição à violência e comportamento foram analisados por meio de questionários autoaplicáveis validados para a língua portuguesa: o *Juvenile Victimization Questionnaire* (JVQ) o *Child Behavior Checklist* (CBCL). No total, participaram do estudo 42 pré-adolescentes (idades entre 10 e 14 anos), alunos de escolas públicas em uma das cidades mais violentas do mundo. Os resultados mostram uma associação (correlação negativa) entre exposição à violência e menos ativação em uma rede frontoparietal do cérebro, incluindo insula, cíngulo anterior e lobo parietal. Estas regiões cerebrais são associadas com atenção e controle inibitório. O estudo sugere que o aprimoramento de funções executivas pode ser um alvo de intervenções voltadas a pré-adolescentes cronicamente expostos a violência.

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LIST OF ABBREVIATIONS

ACC - Accuracy

ADHD – Attention Deficit and Hyperactivity Disorder

ASD – Autism Spectrum Disroder

CBCL - Childhood Behavior Checklist

EF – Executive Functions

ELS – Early Life Stress

fMRI – Functional Magnetic Resonance Imaging

IC – Inhibitory Control

JVQ - Juvenile Victimization Questionnaire

LAC - Latin America and Caribbean

PTSD – Post Traumatic Stress Disorder

RT – Response Time

SES - Socioeconomic status

SN – Saliency Network

SYLLABUS

1. INTRODUCTION

The goal of the present study was to investigate the effects of preadolescent exposure to violence on brain function using functional magnetic resonance imaging (fMRI). Brain function was investigated using a sustained attention and inhibitory control paradigm in fMRI. Preadolescents were from one of the most violent cities in the world, in terms of homicides (WAISELFSZ, 2016a), and violence was assessed by victimization scores from preadolescent's self reports. The instruments used were the Juvenile Victimization Questionnaire 2nd revision (JVQ-R2) and the Childhood Behavior Checklist (CBCL). The study thus combined self-reported indices of exposure to violence and indices of brain function to investigate whether more severe exposure to violence would be associated with changes in brain function in a simple reaction task that tests for inhibitory control and requires preadolescents to sustain attention for a period of time. The goal was to understand whether exposure to violence is significantly affecting brain function associated with a fundamental ability, to maintain attention on a task.

This paper will address the literature on brain development, executive functions (EF) and inhibitory control (IC), the neurobiology of EF and IC, and the neurobiological and behavioral effects of exposure to violence. Subsequently, the results will be presented and discussed in the light of the most recent literature on the effects of exposure to violence on brain function.

2. REVIEW OF LITERATURE

2.1. Brain Development

Human brain development is dynamic and continuous. New experiences, learning, and environmental changes (positive or negative) influence brain function and development since early childhood (MAY, 2011). The balance between positive (such as good parenting skills, higher socioeconomic status (SES), supportive education) and negative (such as violence, drug and alcohol abuse, child maltreatment) environmental factors during child development influences one's ability to achieve their full potential (BEDDINGTON et al., 2008).

Family and community help shape brain development. Of course, there are positive experiences provided by families, communities, school and other social environments that promote development and protection of children and adolescents; but these environments can also be the source of negative experiences and poor outcomes. The literature is rich with developmental studies that examine the effects of various forms of stress on cognition (BIRN, ROEBER, & POLLAK, 2017; GUPTA ET AL., 2017; HANSON ET AL., 2015; LUPIEN, MCEWEN, GUNNAR, & HEIM, 2009; POLLAK, 2005; RAHDAR & GALVÁN, 2014; TAYLOR, EISENBERGER, SAXBE, LEHMAN, & LIEBERMAN, 2006). Investigating the effects that growing up in a violent neighborhood have on brain function is an important approach on understanding how stress changes neurofunctional biology.

Children adapt to life struggles in different forms, and these adaptations are associated with behavioral and neurobiological changes (MOFFITT; TANK, 2013). There is a cascade of chemical events in the body as an adaptive response to stress, and over time this may present as maladaptive characteristics (CERQUEIRA et al., 2007; LUPIEN et al., 2009; MCCRORY; VIDING, 2015; RADLEY et al., 2015); in other words, the excess of chemical responses to stress may become toxic, and result in maladaptive responses such as hyperreactivity to social cues (facial expressions, for example) (MCCRORY; GERIN; VIDING, 2017).

Children who are constantly exposed to stressors, be they a result of domestic violence, extreme poverty, emotional neglect, and other types of difficulties, may adaptively devote more mental resources to recognizing threats and responding to those threats. This shift may limit cognitive resources available to learn, focus on

tasks, control impulses, bond with peers and other constructive pursuits (THOMPSON, 2014). There is only so much “brain power” to go around. Thus, children chronically exposed to violence are at increased risk for a broad range of developmental difficulties, which include behavioral, emotional, and learning problems (BICK; NELSON, 2016; MOFFITT; TANK, 2013; TSAVOUSSIS et al., 2014). These children are also more prone to develop psychiatric disorders such as psychosis, ADHD (Attention Deficit and Hyperactivity Disorder), depression, anxiety among other impairing conditions (FONZO et al., 2016; LUPIEN et al., 2009; M. BANNY et al., 2013).

2.2. Latin America: the world hub for violence and preadolescent violence

The Latin America and Caribbean (LAC) region is home to 8% of the world’s population, but it is where 31% of all homicides in the world take place (THE ECONOMIST, 2017). Of the 50 most violent cities in the world, 43 are in Latin America (20 are in Brazil, including Porto Alegre, which occupies the 42nd position) (CERQUEIRA et al., 2017). Most homicides in the region affect young adults and preadolescents (ages 16-25). Yet these preadolescents are underrepresented in neurocognitive studies of the effects of stress and violence. Schools in LAC have become a violent environment. A study of school violence in six Brazilian cities reported that 84% of students perceived their school environment as violent; and 70% reported being victims of school violence, including physical violence, social discrimination and exclusion, among other violent behaviors (WAISELFSZ, 2016b).

2.3. Executive Functions: Neurobiology and Function

Executive functions (EF) are involved in managing time, paying attention and remembering details, planning and organizing, among other tasks indispensable for day-to-day tasks, such as engaging in learning at school, for example. EF include a spectrum of abilities such as problem solving, self-monitoring, and self-assessment; these abilities overlap with other higher-order mental processes such as attention, inhibitory control, mental flexibility and working memory, which enable goal-directed actions and adaptive responses (DENCKLA, 1994; HUGHES, 2013). Good EF

predict better outcomes, such as positive temperaments, more advanced language and academic skills, better behavioral and social adjustment, and more successful means of coping with stressors, resulting in a better quality of life (BATHELT et al., 2018; DIAMOND, 2013; TAYLOR; CLARK, 2016). These skills depend on the integrity of neural networks that include the prefrontal cortex and the basal ganglia (DIAMOND, 2013; KINSELLA; STOREY; CRAWFORD, 1998; PECHTEL; PIZZAGALLI, 2011; RICHMOND et al., 1967).

EF develop over time across the lifespan, and they can be adversely affected by negative events (DIAMOND, 2013; SUN; BUYS, 2012). Impaired cognitive control is related to poor emotional processing, difficulties in learning, in controlling impulses and in being productive. Deficits in cognitive control are associated with developmental disorders such as ADHD and autism spectrum disorder (ASD) (HUGHES, 2013). It is also related with mood disorders (KNOUSE; BARKLEY; MURPHY, 2013) and schizophrenia (BARCH, 2005; DIAMOND, 2013). Thus, any effect of exposure to violence on EF my translate into effects on skills that are relevant for learning and development (TSAVOUSSIS et al., 2014).

Different forms of chronic stress were shown to decrease gray matter volume and connectivity (ARNSTEN; HAVEN, 2016), and history of early-life stress (ELS) is associated with alterations in emotional and cognitive systems (GUPTA et al., 2017; TEICHER et al., 2016). More specifically, the resulting impairments in executive functions such as working memory (NOBLE et al., 2015; RICHMOND et al., 1967; SPIELBERG et al., 2015), sustained attention (LIM et al., 2016), and innhibitory control (ELTON et al., 2014; JANKOWSKI et al., 2017; LIM et al., 2015; MUELLER et al., 2012; RAHDAR; GALVÁN, 2014) culminate in declined intellectual ability and deteriorated academic performance (PECHTEL; PIZZAGALLI, 2011).

Brain regions that participate in EF tasks are part of the cognitive control network, and include the anterior cingulate cortex/pre-supplementary motor area (ACC/pSMA), dorsolateral prefrontal cortex (DLPFC), inferior frontal junction (IFJ), insular cortex, dorsal pre-motor cortex (dPMC), posterior parietal cortex (PPC) and basal ganglia structures (COLE; SCHNEIDER, 2007; HILTI et al., 2013; METZLER-BADDELEY et al., 2016). These neural components interact closely to implement cognitive control, and are recruited differently according to each environmental demand. Some core EF like response inhibition and working memory are linked and their neural correlates overlap – for instance, the DLPFC and the PPC, that form part

of the central executive network, with the anterior insula and ACC, that form part of the salience network (COLE et al., 2013; LIU et al., 2015; MCNAB et al., 2008) .

For the present study, we will focus on one of the constructs of EF, inhibitory control, and the effects of exposure to violence on the brain's salience network in preadolescents.

2.4. Inhibitory Control

Inhibitory control (IC), also known as response inhibition, is one of the core executive functions. It refers to the ability to control one's attention, behavior, thoughts, and/or emotions to prevail over impulses and habits of thoughts or actions in order to select a more appropriate behavior consistent with the completion of goals (BOECKER; GAUGGEL; DRUEKE, 2013; DIAMOND, 2013; HUGHES, 2013). IC supports flexible and goal-oriented behaviors during decision-making processes, as one decides not to eat a cake in order to keep with one's dietary plan, or decides to stay home and finish an academic work instead of going out to party (ARON, 2011; VERBRUGGEN; LOGAN, 2009). The response suppression promoted by IC depends on interconnected processes that, for instance, allow preadolescents to focus on their homework despite a desire to play, or despite feeling unsfe to study at home (ZHANG; HUGHES; ROWE, 2012).

Human learning depends on the ability to suppress external and internal stimuli. Brain power has to be devoted to reading, understanding, and problem-solving and an impaired ability to concentrate can hamper the success of learning. Inhibitory control also helps preadolescents regulate their emotions and prevents them from acting impulsively, during a particularly impulsive and thrill-seeking period of life (CHAMBERS; TAYLOR; POTENZA, 2003). Disorders typically associated with impairment in response inhibition are addictions (BALER; VOLKOW, 2006; SMITH et al., 2014), ADHD (DIAMOND, 2005; WALSHAW; ALLOY; SABB, 2010), conduct disorder (FAIRCHILD et al., 2009), schizophrenia (BARCH, 2005), obsessive compulsive disorder (OCD) (BERLIN; LEE, 2018; PENADÉS et al., 2007), bipolar disorder (TSITSIPA; FOUNTOULAKIS, 2015) and depression (SNYDER, 2013; TAYLOR TAVARES et al., 2007).

Studies have demonstrated that childhood maltreatment promotes the reorganization of brain networks involved in inhibitory control (ELTON et al., 2014; MUELLER et al., 2010). This may result in increased risk for developing addictions, for acting more impulsively, and for adopting increasingly risky behaviors.

Regions typically involved with inhibitory control are the insula, inferior frontal gyrus, supplementary motor area (SMA) and medial frontal cortex/pre-supplementary motor area (MFC/pSMA) (CAI et al., 2014; DUQUE; OLIVIER; RUSHWORTH, 2013; JHA et al., 2015; LEVY; WAGNER, 2011; MCNAB et al., 2008; NACHEV et al., 2007; SWICK; ASHLEY; TURKEN, 2008); and the success of response inhibition is mediated by the salience network.

2.5. Salience Network: Neurobiology and Function

The salience, or saliency network (SN) is thought to be a collection of regions that are critical to detect and select which stimuli deserves one's attention in order to coordinate neural resources to guide behavior (MENON, 2015; UDDIN, 2017; UDDIN et al., 2017). Relevant stimuli can be internal, such as fear or hunger, or extrapersonal, such as a stop sign when driving or the smell of a freshly baked pie. SN relies on the intrinsic connection between the insula (mostly anterior insula), the dorsal anterior cingulate cortex (dACC), the amygdala, and the basal ganglia (SEELEY et al., 2007; UDDIN, 2015). The SN functions integrating sensory, visceral, emotional and cognitive information having the insular cortex as a hub, thus assisting in the generation of appropriate behavioral responses to salient stimuli (MENON, 2015). The role of the insula in attention will be further discussed below.

2.6. The Insula

The insular cortex is a complex and multipurpose structure, underpinning numerous cognitive functions related to perception, emotion, and interpersonal experience (GASQUOINE, 2014; UDDIN et al., 2017). The insula is part of several brain areas involved with general attention processes (MENON; UDDIN, 2010; POSNER; ROTHBART; VOELKER, 2016; SEELEY et al., 2007), coordinating brain dynamics through its role in the SN. After the detection of the salient stimulus, the

anterior insula enables the suppression of the default mode network and initiates the shift to engage cognitive and task control systems (NAMKUNG; KIM; SAWA, 2017; SRIDHARAN; LEVITIN; MENON, 2008).

The insula, along with the inferior frontal gyrus, preSMA and right middle frontal gyrus, play important role in response inhibition (CAI et al., 2014; JHA et al., 2015; SWICK; ASHLEY; TURKEN, 2008). Studies have shown decreased activation in the insular cortex in attention- and inhibitory control-related tasks in clinical populations whose mental health is affected by violence, such as women with child abuse-related PTSD (Post Traumatic Stress Disorder) (BREMNER et al., 2004). Lesions to the the left insula, in turn, have been associated with detriments in cognitive flexibility in a set-shifting task (VARJAČIĆ et al., 2017).

Adult externalizing behavior, such as aggression and drug abuse, is also associated with effects on insular functional network connectivity (ABRAM et al., 2015). fMRI studies demonstrated atypical intrinsic resting state connectivity in insular regions in developmental disorders, such as autism (DI MARTINO et al., 2014; EBISCH et al., 2011; UDDIN; MENON, 2009), and in mood disorders, such as depression (OLDEHINKEL et al., 2013; UDDIN; MENON, 2009). Depression is also associated with reduced insular cortex volume (SPRENGELMEYER et al., 2011). Insular malfunction is also theorized to have a role in the origin of psychosis in schizophrenia (KAPUR, 2003; PALANIYAPPAN; LIDDLE, 2012).

Child maltreatment, a form of ELS, also has been associated with dysfunction of the insula, SN and its connections (MARUSAK; ETKIN; THOMASON, 2015; VAN DER WERFF et al., 2013). Adults with history of child maltreatment showed reduced connectivity between the insula and limbic structures (VAN DER WERFF et al., 2012). Resiliency, conversely, was associated with increased connectivity within the saliency network (VAN DER WERFF et al., 2013). Preadolescents and children exposed to abuse showed reduced activation in the insula and other attention regions, including left inferior and dorsolateral prefrontal cortex and temporal areas, during a sustained attention task (LIM et al., 2016). The exposure to childhood stress also implied in reduced insular activation along with other SN structures in a reward task (BIRN; ROEBER; POLLAK, 2017), calling attention to the importance of such structures in behavioral patterns of poor decisions and maladaptive risk-taking behaviors.

2.7. fMRI tasks and response inhibition

Functional Magnetic Resonance (fMRI) studies have utilized different tasks to test sustained attention and response inhibition, such as the Stroop task (BREMNER et al., 2004; HALL; O'CARROLL; FRITH, 2010; STROOP, 1935; THOMAES et al., 2012), Stop tasks (CAI et al., 2014; ELTON et al., 2014; LEVY; WAGNER, 2011; MCNAB et al., 2008; MEYER; BUCCI, 2016; MUELLER et al., 2010) and Go/NoGo tasks (GILMAN et al., 2018; MAZZOLA-POMIETTO et al., 2009; MENON et al., 2001). These tasks have in common requiring the participant to withold a prepotent response, which measures selective attention, response inhibition and the hability to select relevant sensory information.

The Change task, also called Stop-Change task, is a variant of the Go/NoGo and Stop tasks, with the difference that it also includes multiasking: besides inhibiting a prepotent response, participants must also replace it with a novel one (JHA et al., 2015; VERBRUGGEN; LOGAN, 2009; VERBRUGGEN; SCHNEIDER; LOGAN, 2008). It requires sustained attention, cognitive flexibility and response inhibition (BOECKER et al., 2011; BOECKER; GAUGGEL; DRUEKE, 2013; LOGAN; BURKELL, 1986; THOMAS et al., 2011). Details of the task will be specified bellow in the *Methods* section.

2.8. Behavioral alterations on fMRI tasks due to the effects of ELS

Studies using the Stop-Change task have shown behavioral differences among different clinical population. Adolescents who were exposed to ELS showed prolonged reaction times compared to controls when switching from the prepotent response ("go") to the alternative response ("change") (MUELLER et al., 2010), the same seen in children with bipolar disorder, suggesting a deficit in response flexibility (MCCLURE et al., 2005). In a sustainned attention task, participants exposed to childhood physical and emotional abuse showed increased errors in the task (LIM et al., 2016), and lower SES was associated with decreased behavioral inhibition in girls in a Go/NoGo task (SPIELBERG et al., 2015).

2.9 Neurobiologial correlates of adversities on fMRI tasks

Besides altered behavioral performance, chronic stress also promotes different patterns of brain functioning. Preadolescents with bipolar disorder showed abnormal activity in ventrolateral and dorsolateral prefrontal cortex, inferior parietal cortex, striatum and in the primary motor cortex during this task (KIM et al., 2012; NELSON et al., 2007). Adolescents exposed to ELS also showed different patterns of brain function, with more activation in the pre- and postcentral gyri, dorsal anterior cingulate gyrus, inferior prefrontal cortex, striatum and posterior insula during correct *change* trials (MUELLER et al., 2010). Effects of ELS were also demonstrated in a similar task, in which adolescents who suffered maltreatment had subcortical hypoactivity during successful trials and subcortical hyperactivity during unsuccessful trials, but maltreated adolescents who received an intervention showed prefrontal hypoactivity during unsuccessful response inhibition (JANKOWSKI et al., 2017).

Prefrontal hypoactivity has also been demonstrated in PTSD and stress-related studies. Exposure to acute stress resulted in reduced activity in the dorsolateral prefrontal cortex in working memory and reward-related tasks (OSSEWAARDE et al., 2011; QIN et al., 2009), and PTSD patients exhibited hypoactivation of the prefrontal cortex during a verbal fluency test (MATSUO et al., 2003). A review of different study designs that aimed to assess impulsivity in cocaine users examined the neural correlates of response inhibition during modified Go/No-Go tasks, demonstrating reduced prefrontal cortex, ACC and salience network function in those individuals (FEIL et al., 2010).

In this fMRI study, we aim to investigate the effects of the exposure of chronic violence, measured by the JVQ (HAMBY et al., 2004, 2005) and the CBCL (BORDIN; MARI; CAEIRO, 1995) on brain connectivity and function using a variation of the Stop-Change task.

3. METHOD

3.1. Participants

Students from five elementary schools from low and high crime indices neighborhoods participated in the study following a citywide invitation by the State Department of Education. All state school principals in the city were invited to a meeting with the researchers. At the meeting, we presented the project and school principals freely signed up for the study. Next, the principals set up meetings at the school with all parents and guardians of children regularly enrolled in the 4th and 5th grades, the last two years of the first stage of elementary school in Brazil; the ages of participants ranged from 10 to 14 years. According to the World Health Organization, adolescency ranges from 10 to 19 years old, and individuals up to the age of fourteen are on the *early* stage, ou pre-adolescency (AMERICAN ACADEMY OF PEDIATRICS, 2003; WORLD HEALTH ORGANIZATION, 2018).

During the meetings, the researchers presented the project, answered questions and handed out informed consent forms to over 300 families. Parents or guardians who consented participation of their sons and daughters later returned the informed consent forms in a sealed, anonymous envelope provided with the form. In total, 140 parents or guardians consented participation in the study. No payment was made to parents or guardians for their participation. Transportation was provided to all participants in all stages of the study. The study was approved by the Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (Certificate of Evaluation of Ethics *CAAE* 57741516.6.0000.5336).

All 140 preadolescents whose parents or guardians consented participation were included in the first stage of the study, which included the evaluations and questionnaires at the schools. Preadolescents were excluded after the first stage due to (1) IQ score below 75, (2) voluntary withdrawal from the investigation, by the guardian or preadolescent; (3) illiteracy or inability to fill out the self-reports and tests; and (4) frequent absence from school during our visits for application of the tests and questionnaires. The total number of preadolescents who completed the second stage of the study was 50. The expressive loss of participants from the initial screening (90 of 140) reflects the challenge of engaging participants and families in at-risk, vulnerable situations and of finding adequate time in the families weekday or weekend schedule to accompany the preadolescents to the Brain Institute.

Socioeconomic status (SES) was investigated using the ABIPEME criteria for classification in Brazil (ABEP, 2008), which provides a score based on schooling and possession of consumer goods. The participants were classified on average as level C1 SES in Brazil (the range was D lower SES to B1 higher SES). Participation was carried out at no cost to participants and we provided free transportation, the neuroradiological reading, and the reading, math, and neuropsychological test scores.

The average age of participants was 11.45 years (SD = 1.01; range 10 to 14 years). IQ was investigated using the Wechsler Abbreviated Scale of Intelligence™ (mean = 95.25; SD= 10.68). The cutoff for participating in the study was an IQ of 75. Victimization was investigated using the Juvenile Victimization Questionnaire. Socioeconomic status (SES), math and reading tests. They answered the abbreviated version of the JVQ and the CBCL. The scoring on the JVQ was set as a parameter to have the students participating in a second stage of the research, in which students with the lowest and highest scores were brought to the Brain Institute. There, they underwent a fMRI exam, had their saliva collected for DNA Methylation analysis and a short piece of their hair collected for cortisol measurement. They also answered the full version of the JVQ. Exclusion criteria were QI under 75, being left-handed, using braces, having hair shorter than 1cm and the presence of brain anatomical alterations. Forty-four children were excluded for either matching those criteria or for not willing to participate in the fMRI exam. From the fourty-eight who completed the full protocol, six were excluded from the fMRI analysis, two due to excessive motion, two that didn’t finish the task, one that presented poor performance and one who had a brain lesion. Analysis were made with resulting 42 participants.

3.2. Chronic Stress and Exposure to Violence: the Juvenile Victimization Questionnaire (JVQ)

The Juvenile Victimization Questionnaire, currently in its 2nd Revision (also called JVQ-R2), is a self-report instrument that assesses 34 different types of interpersonal victimization that may affect children and youth aged 8 to 17 years (FINKELHOR et al., 2005). The JVQ was first administered at the schools, in groups

of 10-20 youths in its reduced format. It was then scored and evaluated. Subsequently, the questionnaire was administered in its full format in an individual interview by a trained member of the clinical research team. The full format of the JVQ is structured to collect more detailed information about each of the types and instances of victimization reported in the reduced format. The JVQ-R2 gathers information on 34 forms of victimization distributed in 5 modules: 9 items for conventional crime, 4 items for maltreatment, 6 items for peer and sibling victimization, 7 items for sexual victimization, and 8 items for witnessing and indirect victimization. It also investigates more recent victimization (*Last Year-LY*) and more chronic exposure to violence (*Lifetime-LT*). For each item, the presence of victimization is scored as 1, the absence is scored zero, generating a sum of victimization events that will be analyzed in total and by module. The current JVQ-R2 full interview was translated to Portuguese with the permission of its authors.

3.3. Behavior Problems – Child Behavior Checklist for ages 6 to 18 (CBCL/6-18)

The version of CBCL/6-18 is a psychological assessment instrument (ACHENBACH; RESCORLA, 2001) used for screening of child and adolescent mental health (BORDIN et al., 2013), allowing to gather information about a large number of psychiatric and somatic symptoms in a short period of time. It's aswered by the parents or caregivers, with an official version for the Brazilian context (BORDIN; MARI; CAEIRO, 1995). The instrument data were imported into the Assessment Data Manager (ADM) software (ASEBA, Burlington, Vermont) to evaluate the raw scores and obtain the clinical, nonclinical, and borderline clinical profiles (ACHENBACH; RESCORLA, 2001). This questionnaire consists of 138 items, with 20 assessing social competence and 118 assessing behavior problems in children and adolescents for ages 6 to 18. This checklist includes 11 subscales assessing symptoms of internalizing (withdrawn, somatic complaints, and anxiety/depressed behaviors) and externalizing problems (delinquent and aggressive behaviors), as well as total problem scores (includes externalizing, internalizing, social, school, thought, and attention problems) (ACHENBACH; EDELBROCK, 1991). The CBCL is not a diagnostic tool, but the resulting scales aim to identify

children at risk of psychiatric disorders, such as ASD, Bipolar Disorder, ADHD, Conduct Disorder, amongst others (HOFFMANN et al., 2016; MBEKOU et al., 2014; NAKAMURA et al., 2009) . It has also been used as a tool to characterize and compare the social competence and behavioral problems displayed by children with chronic illnesses, such as epilepsy (ALMANE et al., 2014).

Internalizing behaviors were associated with reduced hippocampal and amygdala volumes (KOOLSCHIJN et al., 2013). Given the existing correlation between externalizing problems and ELS (JANKOWSKI et al., 2017), internalizing problems and the development of psychopathology (PETTY et al., 2008), and externalizing problems with low self-control and altered ACC activation (MELDRUM et al., 2018), statistical fMRI analysis in this study incorporated the Internalizing and Externalizing Scales, the Total Problems and the Total Social Competence Scale.

3.4. fMRI Paradigm: Change Task

The Change task is an event-related task adapted from previous studies (NELSON et al., 2007). It consists in Go trials and Change trials. Go trials consisted of the presentation of either an X or an O on the screen, to which participants had to press buttons with their left middle and index fingers, respectively. Go trials made up 66% of the trials. Change trials made up 33% of the experiment and consisted of the presentation of a blue square as a visual stimuli, to which participants had to press a button with their right index finger. Since Go trials were more frequent, the task tests the ability of the participant to inhibit the prepotent response (Go - left middle and index fingers) and change it to a different, less frequent response (Change - right index finger). The task lasts 8 min and 3 seconds and has 167 trials, 112 Go and 55 Change. Each trial began with a 500 ms fixation cross at the center of the screen, followed by the stimuli, presented for 1000 ms. The order of the presentation of the stimuli was randomized once, and each participant was presented with the same order. Stimulus presentation was offset by jittered intervals. The jittered intervals between stimuli presentations ranged from 0.75 to 2 sec (in 0.25 sec intervals) and were randomly inserted after each trial. A 6-sec dummy scan was inserted at the beginning of the task to ensure T1 magnetization reached an equilibrium state, and an additional 10-sec rest was inserted at the end. Response times and accuracy were recorded and computed for all trials.

Prior to the scanning session, participants were given an out-of-scanner practice in an MRI simulator (Psychology Software Tools, Pittsburgh, PA) to become acclimated with the scanner environment and noise. The practice session included a shorter version of the task.

3.5. fMRI Parameters

Data was collected on a GE HDxT 3.0T MRI scanner with an 8-channel head coil. Two MRI sequences were acquired: a T1 structural scan (TR/TE = 6.16/2.18ms, isotropic 1mm^3 voxels); and a task-related 8min 3.5s functional FMRI EPI sequence. For the task EPI sequence we used the following parameters: TR = 2000ms, TE = 30ms, 29 interleaved slices, slice thickness = 3.6mm; slice gap = 0.1mm; matrix size = 64 x 64, FOV = 220 x 220mm, voxel size = 3.75 x 3.75 x 3.90mm. During the scan, real-time motion detection was used to monitor the participants. In case participants presented more than 0.9 mm of motion in more than 20 TRs before completing the run, we interrupted the experiment and ran the task again. Only one attempt was made to run the same task if it was stopped due to excessive motion.

3.6. fMRI Analysis

3.6.1. Change task - Correlation between brain imaging data and JVQ Scores

Functional data were preprocessed using AFNI's (http://afni.nimh.nih.gov/) afni_proc.py program (COX, 1996). Preprocessing included slice-time and motion correction, smoothing with a 6-mm FWHM Gaussian kernel, and a nonlinear spatial normalization to 3.0 x 3.0 x 3.0 mm voxel template (HaskinsPedsNL template). TR's with motion outliers (>0.9 mm) were censored from the data. The criteria for exclusion due to head motion were: excessive motion in 20% of the TRs. The average head motion for the participants included in the study was 0.088 (SD 0.048).

First level analysis, convolved with the canonical hemodynamic response function as implemented in AFNI (COX, 1996), included modeling regressors for the conditions for each type of trials (Go and Change).

To investigate the effects of victimization on brain function, a correlation between the JVQ Scores was carried out on individual participants images for all conditions (Change and Go), as implemented in AFNI (COX, 1996). To correct for multiple comparisons, the 3dClustSim program was used to calculate a corrected p-score of < 0.05. The calculation showed that the threshold of p< 0.005 for a minimum cluster size of 71 voxels (3038,8µl) corresponded to a corrected p-score of < 0.05. We report results that survived the threshold of p < 0.005 and a minimum of 71 voxels. The correlation was carried out with the *Lifetime* and the *Last Year* scores for JVQ to investigate the effects of longer exposure and more recent exposure to violence. Subsequently, the correlation was made separately for each JVQ Module, to investigate the effects of each type of violence on brain function. Correlation was also made with the CBCL Scales for Externalizing and Internalizing behaviors, and also with the Total Problems Score.

3.6.2. Betas

The average betas for functional regions of interest were extracted for individual participants for the regions of the insula, parietal and prefrontal cortex. These regions were selected based on the results for the correlation analysis between brain function and exposure to violence (see Results).

3.6.3. Behavioral data analysis

Participants responded to the task using mice buttons. The response and response times were recorded using E-Prime (Psychology Software Tools, Pittsburgh, PA) for all trials. Behavioral data was analyzed using Spearman's rho correlation for significant association between response times (RT) and accuracy (ACC) on the task and the JVQ scores.

To test if the length of the task would have an effect on the participants' performances, the mean ACC and RT of each trial were correlated with the order of the presentation of the trials. To test the effects of chronic stress on the performance over time, each participant had his RT and ACC for each trial correlated (Pearson's) with the order of presentation of each trial in the experiment. The resultant *r* for each participant was then correlated with the JVQ scores.

8. RESULTS

8.1. Chronic Exposure to Violence

Table 01 shows descriptive statistics (mean ± SD) of our sample for each domain module of JVQ-R2 full interview, as well as for the total score. The majority of preadolescents (36 participants, 85.7%) had experienced at least one form of victimization over the life span, and 31 (73.8%) reported being exposed to violence over the last year.

The most common type of violence exposure was conventional crime (69%), followed by witnessing/indirect forms of violence (59.5%).

Participants, Exposure to Violence and Types of Exposure					
	n	**%**	**Min**	**Max**	**Mean (SD)**
Age	42		09	14	11.34 (1.06)
Gender	42				
Female	16	38.1			
Male	26	61.9			
IQ	42		75	114	95.55 (10.45)
SES	42		D	B1	C1
JVQ Lifetime	36	85.7	1	20	5.25 (4.18)
Conventional crime	29	69	1	7	2.55 (1.52)
Maltreatment	13	31	1	2	1.23 (0.44)
Peer and sibling victimization	14	33.3	1	4	1.71 (1.21)
Sexual victimization	04	9.5	1	2	1.25 (0.5)
Witnessing and other exposure to violence	25	59.5	1	5	2.64 (1.44)
JVQ Last Year	31	73.8	1	18	3.35 (3.51)
CBCL Internalizing Problems	40	95.2	3	40	17.67 (10.34)
CBCL Externalizing Problems	40	95.2	5	45	19.67 (9.37)
CBCL Total Problems	40	95.2	13	125	58.28 (27)

CBCL Social Competence Scale	39	92.8	3	22	12.94 (3.77)

Table 01. Descriptive statistics for the total sample. On the JVQ and CBCL scoring, *n* refers to the number of participants that were exposed to at leats one type of violence and presented at least one . SD: Standard deviation. SES: Socioeconomic Status.

Spearman's *rho* correlation was carried out between the JVQ Scores and CBCL Scales, and there was a significant negative correlation between the JVQ Modules 1 (Conventional Crime) and 2 (Maltreatment) with the CBCL Total Social Competence Score (p=0.019 and p=0.024, respectively). The Social Competence Score assesses social interaction patterns, for instance if they interact well with other children and family members, how many close friends they have and how much time they spend together, and their level of independency when playing or working alone (BORDIN et al., 2013). Low scores on this scale suggest there might be an effect of exposure to specific types of violence (conventional crime and maltreatment).

8.2. fMRI Results

8.2.1. Effects of violence exposure

Results show that exposure to violence was associated with deactivation of a frontal-parietal-insular network of areas. Higher JVQ *Lifetime* scores, which assess the exposure to violence over the life span, correlated negatively with activation of a bilateral network of areas that included the insula, parietal cortex, and right superior frontal cortex (see Table 02 and Figure 01), for both Go and Change trials combined (all conditions). The correlation with JVQ *Last Year* scores, which assess more recent exposure to violence, showed deactivation of frontal, parietal and temporal areas (Table 03).

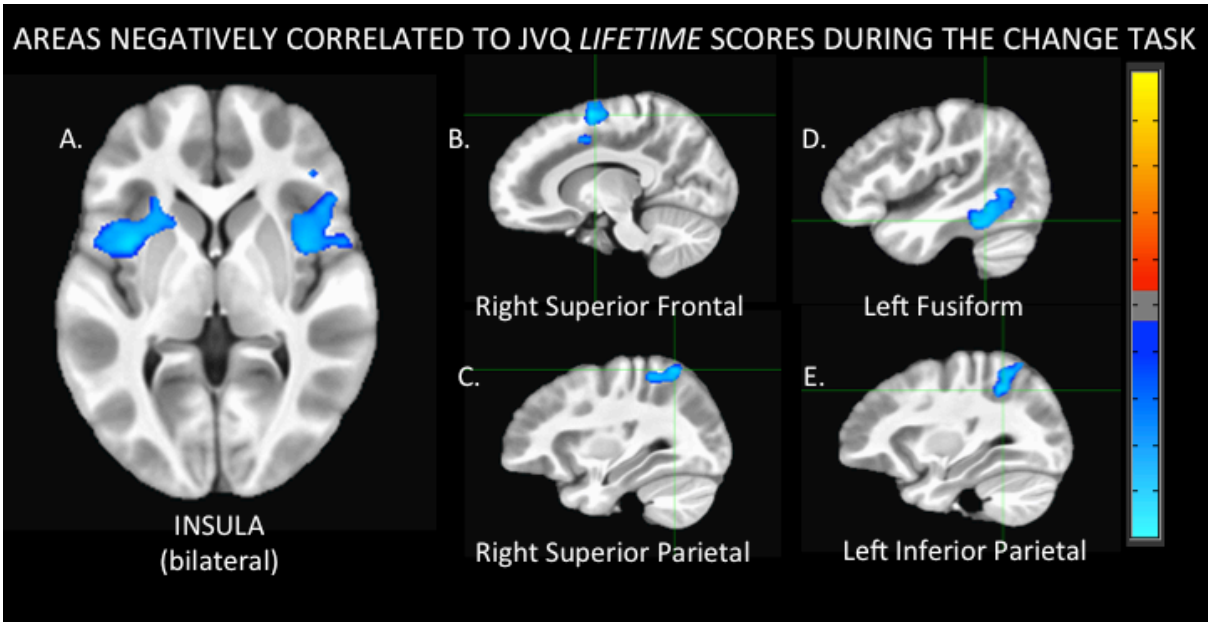


Figure 01. Negative correlation for JVQ Lifetime scores with all conditions (Go and Change) in the Change task. Clusters significant at $p < 0.05$ corrected for multiple comparisons (which corresponded to a threshold of 71 voxels and $p < 0.005$ in AFNI). A. Axial slice rendering for the correlation results for Right Insula (x = 35, y = 5, z= 6) and Left Insula (x = - 35, y = 5, z = 6). B. Sagital slice for Right Superior Frontal (x = 10, y = - 2, z = 58). C. Sagital slice for Right Superior Parietal (x = 28, y = - 54, z = 58). D. Sagital slice for Left Fusiform (x = - 42, y = - 43, z = - 11). E. Sagital slice for Left Inferior Parietal (x = -28, y = - 47, z = 41).

Areas negatively correlated to JVQ LT Scores during the Change Task

REGION	PEAK MNI COORDINATES (x ,y , z)			BA	No. of voxels
Right Superior Frontal	**10**	**- 2**	**58**	**6**	**341**
Right Precentral					39
Right Superior Frontal					65
Right Caudal Middle Frontal					13
Right Caudal Anterior					5
Right Postcentral					3
Right Paracentral					3
Left Superior Frontal					81
Left Posterior Cingulate					28
Left Caudal Middle Frontal					11
Left Caudal Anterior					31

Righ Insula	**35**	**5**	**6**	**13**	**103**
Right Pars Opercularis					61
Right Superior Temporal					13
Right Pars Triangularis					11
Right Insula					9
Right Precentral					3
Right Pars Orbitalis					2
Right Postcentral					1
Right Rostral Middle Frontal					1
Right Superior Parietal	**28**	**- 54**	**58**	**7/40**	**75**
Right Superior Parietal					42
Right Postcentral					11
Right Inferior Parietal					22
Left Insula	**- 35**	**5**	**6**	**13**	**207**
Left Pars Opercularis					81
Left Insula					34
Left Superior Temporal					24
Left Precentral					19
Left Putamen					10
Left Lateral Orbito Frontal					6
Left Caudal Middle Frontal					2
Left Pars Triangularis					1
Left Rostral Middle Frontal					1
Left Caudate					1
Left Inferior Parietal	**- 28**	**- 47**	**41**	**7**	**105**
Left Superior Temporal					65
Left Inferior Parietal					22
Left Postcentral					12
Left Precuneus					5
Left Fusiform	**- 42**	**- 44**	**- 12**	**37**	**77**
Left Fusiform					41
Left Inferior Temporal					28
Left Middle Temporal					3
Left Inferior Parietal					1

Table 02. Negative correlation between JVQ Lifetime scores and activation for the whole task (Change and Go trials combined) in areas involved in cognitive control, attention and memory. This table shows the areas that presented deactivation during the task. Voxel count for white matter not included. LT: Lifetime. BA: Brodmann Area.

Areas negatively correlated to JVQ LY Scores during the Change Task			
REGION	**PEAK MNI COORDINATES (x ,y , z)**	**BA**	**No. of voxels**

Right Superior Frontal	**14**	**2**	**62**	**6**	**514**
Right Precentral					85
Right Superior Frontal					80
Right Caudal Middle Frontal					21
Right Caudal Anterior Cingulate					18
Right Posterior Cingulate					9
Right Postcentral					4
Right Paracentral					3
Right Supramarginal					3
Left Superior Frontal					100
Left Precentral					49
Left Posterior Cingulate					38
Left Caudal Middle Frontal					18
Left Caudal Anterior Cingulate					4
Right Superior Parietal	**28**	**- 40**	**51**	**40**	**122**
Right Superior Parietal					60
Right Postcentral					29
Right Precuneus					15
Right Inferior Parietal					11
Left Precuneus	**- 7**	**- 72**	**51**	**7**	**650**
Right Lingual					85
Right Cuneus					34
Right Cerebellum					54
Right Precuneus					16
Right Pericalcarine					14
Right Isthmus Cingulate					12
Right Fusiform					8
Left Precuneus					89
Left Cuneus					69
Left Superior Parietal					63
Left Cerebellum					95
Left Fusiform					22
Left Lingual					18
Left Inferior Parietal					12
Left Pericalcarine					9
Left Isthmus Cingulate					8
Left Postcentral					8
Left Superior Temporal	**- 56**	**- 2**	**- 1**	**21/22**	**74**
Left Superior Temporal					58
Left Middle Temporal					13
Left Postcentral					2
Left Inferior Temporal	**- 42**	**- 37**	**- 8**	-	**72**
Left Fusiform					33
Left Inferior Temporal					32
Left Cerebellum Cortex					3
Left Middle Temporal					1

Table 03. Negative correlation between JVQ Last Year scores and activation for the whole task (Change and Go trials combined) in areas involved in cognitive control, attention and memory, but not in the insula. This table shows the areas that presented deactivation during the task. Voxel count for white matter not included. LY: Last Year. BA: Brodmann Area.

8.1.2. Type of victimization - JVQ Modules

To further investigate the type of violence exposure that affects brain function, the same analysis was made with each separated JVQ module. There was no

significant correlation for the whole task (Change and Go trials combined) with modules 1 (conventional crime) and 2 (maltreatment), but there was a negative correlation between scores on modules 3 (peer and siblings victimization), 4 (sexual victimization) and 5 (witness/indirect victimization) (Tables 04, 05 and 06).

Areas negatively correlated to JVQ Peer and Siblings Victimization Scores during the Change Task

REGION	PEAK MNI COORDINATES (x ,y , z)			BA	No. of voxels
Right Pars Opercularis	**38**	**12**	**6**	**13**	**158**
Right Pars Opercularis					94
Right Putamen					26
Right Insula					26
Right Superior Temporal					13
Right Precentral					8
Right Lateral Orbitofrontal					8
Right Pars Triangularis					4
Right Pars Orbital					2
Right Postcentral					2
Right Superior Parietal	**42**	**- 47**	**58**	**40**	**91**
Right Inferior Parietal					55
Right Superior Parietal					15
Right Postcentral					4
Right Supramarginal					1
Left Insula	**- 35**	**5**	**6**	**13**	**130**
Left Pars Opercularis					74
Left Insula					27
Left Superior Temporal					9
Left Precentral					8
Left Lateral Orbitofrontal					4

Table 04. Negative correlation between Peer and Siblings JVQ scores and activation for the whole task (Change and Go trials combined) in areas of the insula and inferior frontal gyrus (pars opercularis). Voxel count for white matter not included. BA: Brodmann Area.

Areas negatively correlated to JVQ Sexual Victimization Scores during the Change Task

REGION	PEAK MNI COORDINATES (x ,y , z)	BA	No. of voxels

Areas negatively correlated to JVQ Sexual Victimization Scores during the Change Task

REGION	PEAK MNI COORDINATES (x ,y , z)			BA	No. of voxels
Right Superior Frontal	**14**	**2**	**62**	**6**	**281**
Right Superior Frontal					55
Right Precentral					19
Right Caudal Anterior Cingulate					16
Right Caudal Middle Frontal					1
Left Superior Frontal					55
Left Caudal Middle Frontal					35
Left Caudal Anterior Cingulate					23
Left Precentral					17
Right Superior Parietal	**28**	**- 40**	**55**	**40**	**123**
Right Superior Parietal					64
Right Postcentral					38
Right Inferior Parietal					11
Right Precuneus					5
Right Putamen	**24**	**9**	**- 1**	**-**	**89**
Right Putamen					42
Right Pars Opercularis					19
Right Insula					16
Right Superior Temporal					9
Right Caudate					1
Left Cuneus	**0**	**- 72**	**20**	**18/31**	**773**
Right Lingual					121
Right Fusiform					86
Right Pericalcarine					41
Right Cerebellum Cortex					39
Right Cuneus					37
Right Inferior Temporal					23
Right Lateral Occipital					22
Right Isthmus Cingulate					19
Right Inferior Parietal					14
Right Hippocampus					9
Right Thalamus					6
Right Lateral Ventricle					5
Right Precuneus					2
Right Superior Parietal					1
Left Cuneus					83
Left Lingual					51
Left Pericalcarine					30
Left Isthmus Cingulate					14
Left Cerebellum Cortex					12
Left Precuneus					9
Left Hippocampus					5
Left Fusiform					5
Left Lateral Ventricle					3
Left Thalamus					1
Left BanksSTS	**- 52**	**- 30**	**6**	**22/21**	**221**
Left Superior Temporal					42
Left Putamen					36

Areas negatively correlated to JVQ Sexual Victimization Scores during the Change Task					
REGION	**PEAK MNI COORDINATES (x ,y , z)**			**BA**	**No. of voxels**
Left Insula					24
Left Pars Opercularis					23
Left Rostral Middle Frontal					12
Left Middle Temporal					9
Left Lateral Orbitofrontal					6
Left Amygdala					4
Left Pars Triangularis					4
Left Caudate					3
Left Pallidum					1
Left Precentral					1
Left Pars Triangularis	**- 24**	**23**	**16**	-	**221**
Left Superior Temporal					42
Left Putamen					36
Left Insula					24
Left Pars Opercularis					23
Left Rostral Middle Frontal					12
Left Middle Temporal					9
Left Lateral Orbitofrontal					6
Left Amygdala					4
Left Pars Triangularis					4
Left Caudate					3
Left Pallidum					1
Left Precentral					1

Table 05. Negative correlation between Sexual Victimization JVQ scores and activation for the whole task (Change and Go trials combined) in parietal and temporal areas, besides the insula and inferior frontal gyrus, and also in left lymbic structures (amygdala and hippocampus). Voxel count for white matter not included. BA: Brodmann Area.

Areas negatively correlated to JVQ Witness/Indirect Victimization Scores during the Change Task

REGION	PEAK MNI COORDINATES (x ,y , z)			BA	No. of voxels
Right Superior Frontal	**10**	**- 2**	**58**	**6**	**446**
Right Superior Temporal					73
Right Paracentral					58
Right Posterior Cingulate					33
Right Caudal Anterior Cingulate					21
Right Precentral					14
Right Postcentral					4
Right Precuneus					3
Left Superior Frontal					42
Left Posterior Cingulate					35
Left Caudal Anterior Cingulate					27
Left Paracentral					6
Left Isthmus Cingulate					1
Right Pars Opercularis	**38**	**5**	**6**	**13**	**108**
Right Pars Opercularis					36
Right Superior Temporal					31
Right Insula					21
Right Precentral					7
Right Putamen					4
Right Middle Temporal					2
Right Amygdala					1
Right Supramarginal	**31**	**- 30**	**- 20**	**-**	**101**
Right Supramarginal					39
Right Superior Temporal					29
Right Bankstats					8
Right Transverse Temporal					5
Right Inferior Parietal					2
Right Insula					2
Left Superior Temporal	**- 45**	**- 37**	**23**	**13**	**1041**
Right Cerebellum Cortex					99
Right Fusiform					65
Right Lingual					64
Right Thalamus					35
Right Parahippocampal					4
Right Lateral Ventricle					4
Right Isthmus Cingulate					4
Right Pericalcarine					3
Right Hippocampus					3
Right Lateral Occipital					2
Ritgh Inferior Temporal					2
Left Cerebellum Cortex					133
Left Fusiform					72
Left Superior Temporal					49
Left Supramarginal					36
Left Lingual					33
Left Inferior Temporal					19
Left Hippocampus					19
Left Parahippocampal					18

Areas negatively correlated to JVQ Witness/Indirect Victimization Scores during the Change Task					
REGION	**PEAK MNI COORDINATES (x ,y , z)**			**BA**	**No. of voxels**
Left Transverse Temporal					11
Left Thalamus					6
Left Isthmus Cingulate					6
Left Insula					6
Left Putamen					3
Left Postcentral					3
Left Lateral Ventricle					2
Left Inferior Lateral Ventricle					2
Left Bankstats					2
Left Precuneus					1
Left Pericalcarine					1
Left Middle Temporal					1
Brein Stem					73
Left Lateral Orbitofrontal	**- 28**	**16**	**- 8**	**47/13**	**207**
Left Insula					40
Left Pars Opercularis					34
Left Lateral Orbitofrontal					33
Left Superior Temporal					21
Left Amygdala					18
Left Precentral					16
Left Medial Orbitofrontal					5
Left Superior Parietal	**- 31**	**- 51**	**55**	**40**	**108**
Left Precuneus					48
Left Superior Parietal					45
Left Inferior Parietal					7
Peft Paracentral					1
Left Postcentral					1

Table 06. Negative correlation between Witness/Indirect Victimization JVQ scores and activation for the whole task (Change and Go trials combined) in bilateral temporal, parietal, limbic areas.. Voxel count for white matter not included. BA: Brodmann Area.

There were no significant findings when analyzing the Change trials vs. the Go trials in correlation with the JVQ scores, nor between correct Change answers versus incorrect Change answers.

8.1.3. Behavior effects - CBCL

Results showed deactivation of a frontal network of areas associated with internalizing behaviors on the CBCL. Higher scores on the Internalizing Behaviors Scale correlated negatively with activation of a bilateral network of frontal areas (see figure 02 and table 07), for the whole Change task (Go and Change trials combined).

There was no statistically significant association between Externalizing Behaviors and Total Problems on the CBCL Scale and brain function during the task.

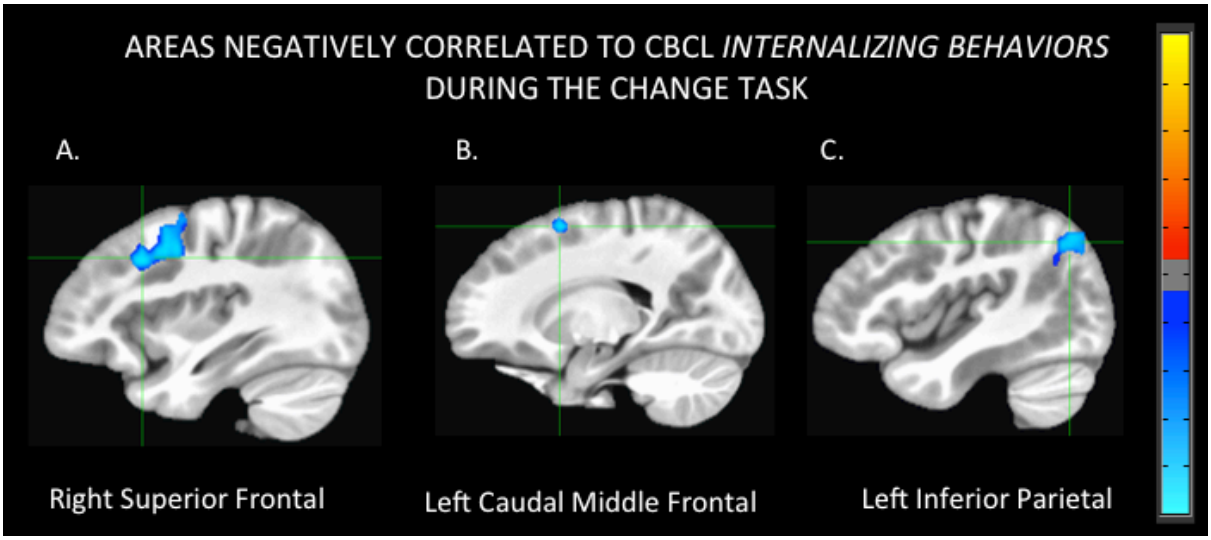


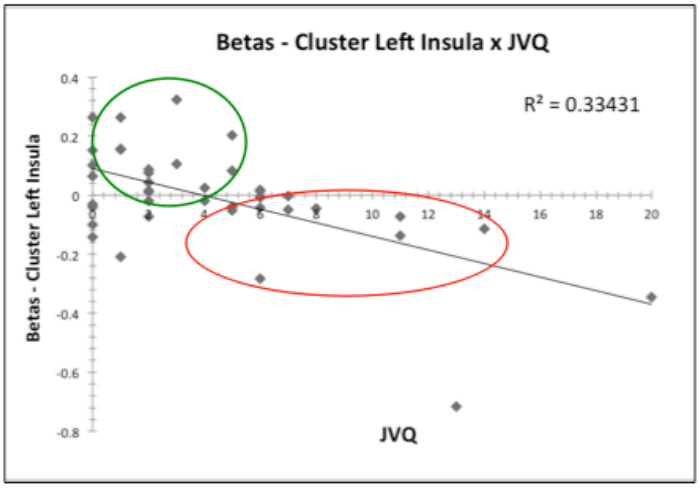
Figure 02. Negative correlation for CBCL Internalizing Behaviors with all conditions (Go and Change) in the Change task. Clusters significant at $p < 0.05$ corrected for multiple comparisons (which corresponded to a threshold of 71 voxels and $p < 0.005$ in AFNI). A. Sagital slice for Right Superior Frontal (x = 17, y = 9, z = 55). B. Sagital slice for Left Caudal Middle Frontal (x = - 31, y = 16, z = 37). C. Sagital slice for Left Inferior Parietal (x = - 38, y = - 65, z = 41).

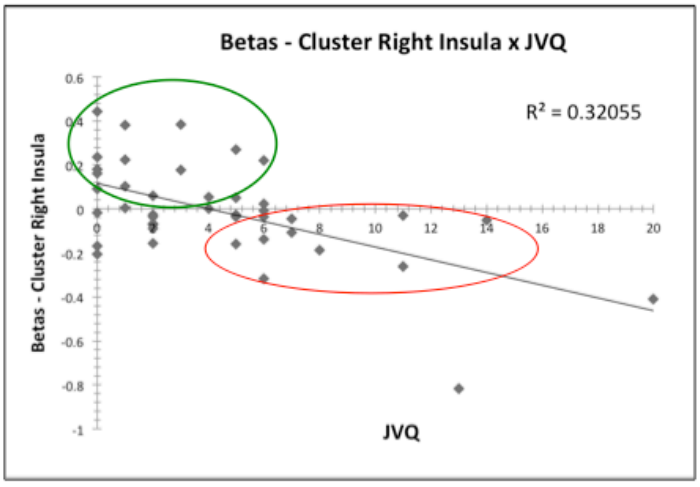
Areas negatively correlated to CBCL Internalizing Behaviors						
	REGION	**PEAK MNI COORDINATES (x, y, z)**			**BA**	**No. of voxels**
RIGHT						
	Superior Frontal	17	9	55	6	97
LEFT						
	Caudal Middle Frontal	- 31	16	37	9	143
	Inferior Parietal	- 38	- 65	41	39/7	91

Table 07. Negative correlation between Internalizing Behaviors on the CBCL Scales and activation for the whole task (Go and Change trials combined) in bilateral frontal areas. BA: Brodmann Area.

8.1.4. Betas

The average betas for functional regions of interest were extracted for individual participants for the regions of the insula and prefrontal cortex. These betas were correlated with the JVQ-R2 scores and CBCL scales to investigate relative activation or deactivation for each participant versus their score for exposure. The results show that most high-exposure JVQ scores were associated with negative betas for the insula and the frontal cortex clusters, and that higher scores on the Internalizing Scale of the CBCL were associated with negative betas for the frontal cluster. The results are shown in Figures 03 and 04 below.





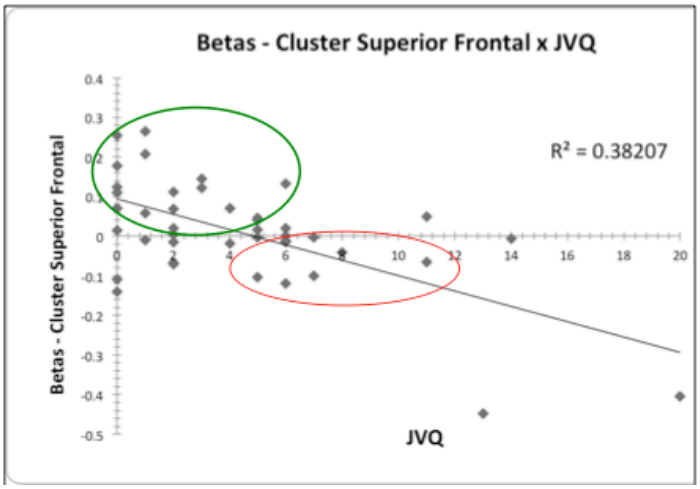


Figure 03. Correlation between JVQ *Lifetime* score and the betas extracted for each main cluster of areas. Green elipses highlight low exposure, positive betas (activation); Red ellipses highligh high exposure, negative betas (deactivation) showing that high-exposure youths, in fact, had deactivation of the brain areas identified in the correlation analyses.

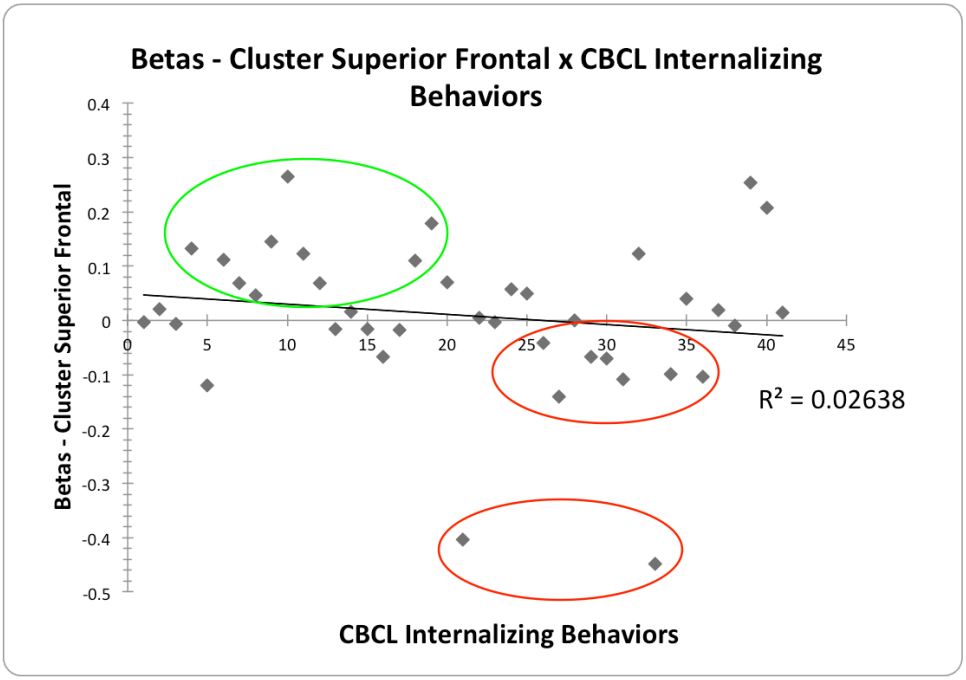


Figure 04. Correlation between CBCL Internalizing Behaviors and the betas extracted for the frontal cluster. Green elipse highlights less internalizing behaviors and positive betas (activation); Red ellipses highligh more internalizing behaviors and negative betas (deactivation) showing that youths with more internalizing behaviors, in fact, had deactivation of the brain areas identified in the correlation analyses.

8.1.5. Behavioral Results

Forty-six participants completed the task and had their data analyzed. The mean accuracy (ACC) for the whole group was 0.83 (SD 0.13) and mean response time (RT) was 636.7 (SD 58.7). For the *Change* trials, mean ACC was 0.88 (SD 0.09) and mean RT was 625.44 (sd 64.32). For the *go* trials, mean ACC was 0.80 (sd 0.17) and mean RT was 642.49 (sd 60.79). When correlated to the JVQ scores and CBCL Scales, there was no statistically significant findings.

Besides testing for inhibitory control and task-switching skills, the task also requires sustained attention, because the participant must focus on the taks for over 8 minutes. As expected (HILTI et al., 2013), the mean accuracy for all participants decays over the experiment ($p<0.001$), as the response time increases ($p=0.005$) (Figure 05).

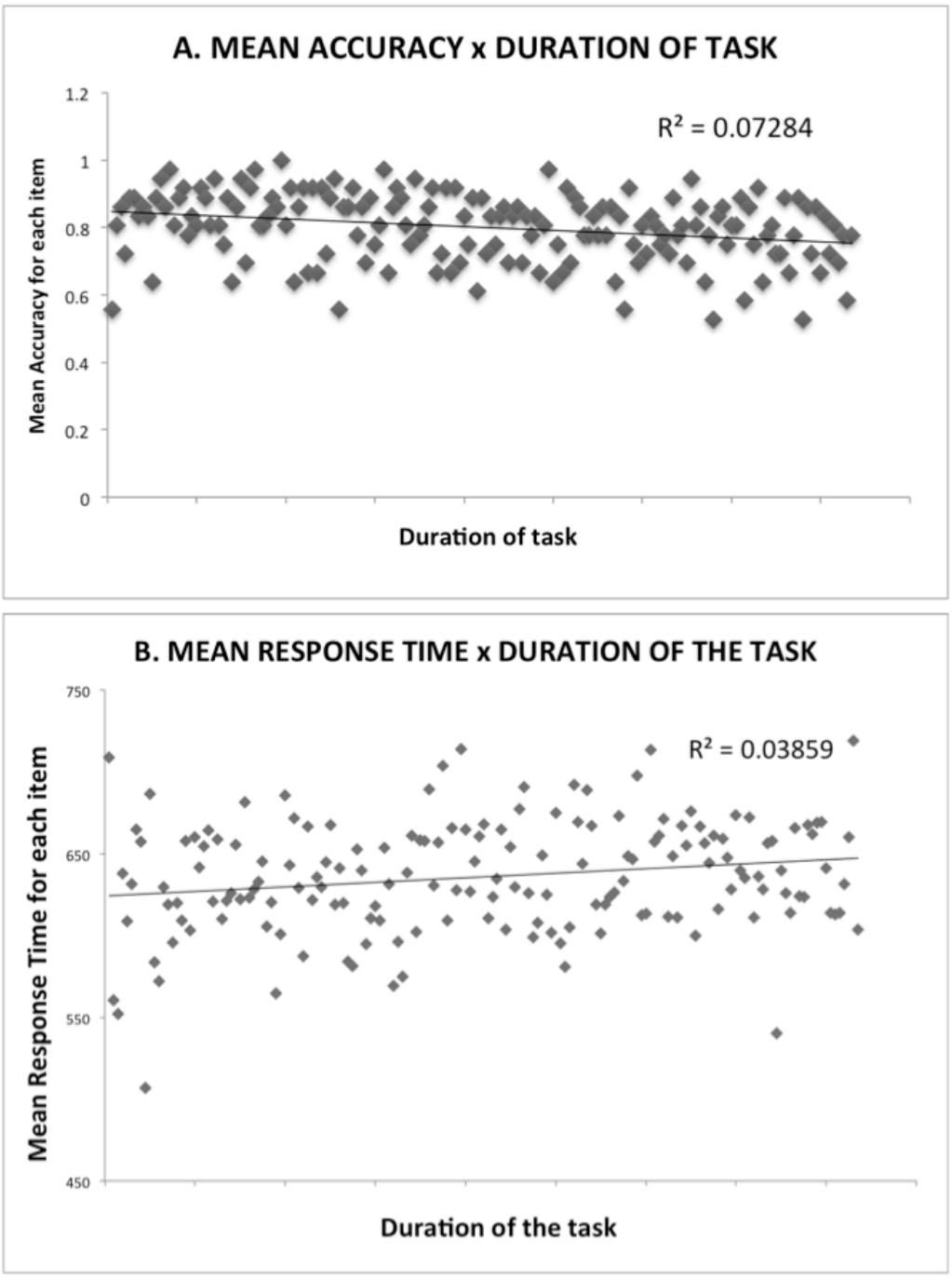


Figure 05. Effect of time on sustained attention. A. The mean accuracy for each trial decays over the experiment ($p < 0.001$). B. The mean response time for each trial increases ($p < 0.01$).

To correlate performance over the task with violence exposure, each participant had his RT and ACC for each trial correlated (Pearson's) with the order of presentation of each trial in the experiment. The resultant *r* for each participant was then correlated with the JVQ scores. Even though there is a negative correlation, it was not statistically significant.

9. DISCUSSION

The present study suggests that exposure to violence has an effect on preadolescent's brain function associated with IC and sustainned attention. The higher the indices that reflect lifetime exposure to violence, the less activation on areas associated with inhibitory control, specifically, the bilateral insula and inferior frontal gyrus (pars opercularis), typically activated in EF tasks (ARON, 2011; BOECKER et al., 2011; LEVY; WAGNER, 2011).

The literature is rich with studies that investigate maltreatment, abuse, and other puncutal forms of ELS in brain EF such as working memory, also emotional and reward processing (ARNSTEN, 2011; BIRN; ROEBER; POLLAK, 2017; HERRINGA et al., 2013). Recent reviews show evidence of different effects of ELS on the brain (BICK; NELSON, 2016; JANKOWSKI et al., 2017; MCCRORY; GERIN; VIDING, 2017), associating early deprivation with more activation in the amygdala to fearful and angry faces; maltreatment with changes in grey matter volume in the amygdala; and different forms of abuse with decreased activation in the insula and hippocampus during reward anticipation and different patterns of connectivity among brain areas.

On the other hand, few studies have specifically investigated inhibitory control in preadolescents exposed to violence, and the resulst are heterogenous. Specific investigations of IC and sustainned attention showed that the brains of children who experienced deprivation in institutionalized care (MUELLER et al., 2010) had a hyperactivation of the inferior frontal gyrus, anterior cingulate cortex, precentral and postcentral gyri, insula, caudate, and putamen; maltreated adolescents with PTSD, in turn, presented middle frontal hypoactivation and medial frontal, inferior temporal, insular and occipital hyperactivation (CARRION et al., 2008); finally, severely abused children showed reduced activation in the ventral and dorsal frontal attention regions of left inferior frontal cortex, anterior insula and dorsolateral-prefrontal cortex (LIM et al., 2016).

Though the results from different studies show varied modulations of activation and different cortical areas affected by violence, one pattern is clear: there is atypical recruitment of cortical areas associated with executive functions in youth exposed to violence. Our results, in this sense, corroborate the literature and show a dimensional effect of exposure to violence and evidence for atypical recruitment of a

network of areas in victimized preadolescents during response inhibition. The areas that are deactivated in association with exposure are mostly activated in preadolescents with lower or no exposure, as shown in Figure 03.

In our study, the duration of the exposure to violence also showed different effects on preadolescent's brain function. While lifetime victimization was associated with deactivation of the insular cortex, bilaterally, recent exposure to violence (measured by the JVQ *Last Year* scores) was not. The effect on the insular cortex was only due to the chronic, lifetime exposure to violence. In contrast, recent victimization was associated with deactivation in the anterior and posterior cingulate cortex and in a bilateral temporal-parietal network. Deactivation on bilateral superior frontal cortex was identified in both correlations. These regions are also associated with cognitive control, behavioral flexibility, emotional regulation and working memory (RADLEY et al., 2015).

Importantly, the type of victimization influenced these results. From the five JVQ modules, only three showed a significant negative correlation with brain activation: Peer and Siblings victimization, Sexual victimization and Witness/Indirect victimization. Deactivation in limbic structures, such as the amygdala, hippocampus and parahippocampal cortex was correlated with sexual and indirect victimization.

The relationship between exposure to violence and behavior was demonstrated by the negative correlation between CBCL Total Social Competence Score and the JVQ Conventional Crime and Maltreatment modules. That means that social skills are being compromized due to exposure to maltreatment and conventional crime. Moreover, preadolescent's behavior was also associated with atypical recruitment of cortical areas of the brain. Higher CBCL Internalizing Behaviors (which includes symptoms from the anxious/depressed, withdrawn/depressed and somatic complaints subscales) were associated with deactivation on bilateral frontal areas that are related to working memory and other EF (BICK; NELSON, 2016). Is brain function affected by altered behavior, or is it the other way round? This study cannot answer this question, but raises possibilities for further investigation.

It is important to mention that the brain areas found in this study to be less activated during the task do not form a specific functional network; they are rather components of the Salience Network and Fronto-Parietal Network, which are both part of the Control Network (COLE; SCHNEIDER, 2007; HILTI et al., 2013). Brain

systems and functional networks are still not yet fully mapped, and are stil subject of research. Although major components of resting-state (that is, when the brain is not involved in any particukar task) networks are anatomically connected, there is still a large number of functional connections between brain regions that are not direct correspondents of an anatomical pathway (SPORNS; TONONI; KÖTTER, 2005). In this sense, studies like this one contribute to the building of a better understanding on brain connectivity systems (SPORNS, 2011).

Inhibitory control is thought to improve with age due to increasing activity in the frontostriatal circuits (MARSH; GERBER; PETERSON, 2008). The deactivation of large bilateral networks associated with IC and sustainned attention shown in this study suggests a deleterious effect of exposure to violence on brain development. Even though task performance was not significantly impaired in association with violence, the disengagement of the insular cortex might imply deterioration in connectivity and/or function along the SN; if dysruption of the SN in preadolescents becomes permanent, or is not targeted, it is possible they may be at risk for developing EF defficits.

The question emerges as to what adaptive mechanism would be associated with the deactivation of the insular-frontal network. Are preadolescent's brains "shutting down" due to a lifetime of exposure to violence? Are preadolescent's brains overloaded with filtering and focusing attention to survive? The present study cannot answer these questions, nor can it state that the effects of exposure will not disappear with age, but the results do suggest that there may be a maladaptive coping mechanism of the brain taking hold. If brain function associated with the ability to control inhibition and sustain attention is severely impaired by exposure to violence, one can only begin to speculate the school and social-life effects that may follow, such as impaired learning and studying abilities, impaired social abilities, poor impulse control and the impossibility of reaching the full potential as an adult.

The present study shows, for the first time, that exposure to violence is associated with deactivation of brain networks associated with response inhibition during a task that taps into this skill. The implications of this effects have to be investigated longitudinally, rather than cross-sectionally as the present study does. However, the results show that the brains of preadolescents who have been exposed to more chronic levels of violence have a significant disengagement of areas that, for preadolescents who are less exposed, are active during the inhibitoy control task.

Further analysis should be made to investigate the effects of exposure to violence in preadolescent's brain structure and resting state connectivity. Our findings provide evidence that youth victimization and exposure to violence alters the neural patterns underlying executive functioning, indicating possible targets to preventive interventions.

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ANEXOS

Anexo 01 – Prova de submissão do artigo “An fMRI investigation of preadolescent exposure to violence and inhibitory control: decreased activation of frontal and parietal regions associated with violence and increased latency in response”.

An fMRI investigation of preadolescent exposure to violence and inhibitory control: decreased activation of frontal and parietal regions associated with violence and increased latency in response.

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Brain function and development are influenced by experiences (May, 2011). High levels of stress are associated with alterations in mental health and behavior and are coupled with alterations in brain function and structure. In children, high levels of stress (early life stress) are associated with more risk-taking behavior in adulthood and alterations in function in the brain's reward circuitry (Birn, Roeber, & Pollak, 2017), with more somatization and alterations in brain wiring (Gupta et al., 2017), and with more behavior problems and alterations in limbic system function and structure (Hanson et al., 2015; Lupien, McEwen, Gunnar, & Heim, 2009). In adolescents, high levels of stress affect mental health, cognition, and brain function (Buchweitz et al., 2019; Lupien, McEwen, Gunnar, & Heim, 2009; Rahdar & Galván, 2014).

Adolescence is a period of heightened susceptibility to social context (Schriber & Guyer, 2016) and it is the peak period for emergence of psychiatric disorders (Burke Quinlan et al., 2018; Machado et al., 2016; Paus, Keshavan, & Giedd, 2008; Toazza et al., 2016); but adolescence is also second window of opportunity for reaping strong dividends in investments in health and educational policies (Choudhury, 2017; Patton et al., 2016). It is a critical juncture for life-changing decisions (Novella, Repetto, Robino, & Rucci, 2018; UNICEF, 2017) while the brain is highly sensitive to stress-induced neurobehavioral dysfunctions (Eiland & Romeo, 2013).

The effects of adolescent exposure to violence on brain function are poorly understood. The neurocognitive evidence of the effects of violence on adolescent brain function is especially scarce in Latin America and the Caribbean (LAC) (Buchweitz et al., 2019). Most homicides in the world occur in LAC, and they affect youths disproportionately (CERQUEIRA et al., 2018). LAC is also home to high percentages of NEET[1] youths (Novella et al., 2018), The goal of the present study was to investigate exposure to violence and its effects on brain function in an inhibitory control task. The study was carried out with Latin-American preadolescents in an urban setting among the most dangerous in the world (CERQUEIRA et al., 2018).

Inhibitory control and the adolescent brain

[1] Youths Not in Employment, Education or Training (NEET)

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Executive functions are umbrella for abilities associated with controlling and coordinating thoughts and action. They include, for example, inhibitory control and mental flexibility, which enable goal-directed actions and adaptive responses (Denckla, 1994; Fuster, 2000; Hughes, 2013; Stocco, Lebiere, O'Reilly, & Anderson, 2012). Brain imaging has shown that these functions are underpinned by a distributed, anterior-posterior network that includes lateral prefrontal cortex, anterior cingulate cortex, medial prefrontal regions, posterior parietal cortex, and the basal ganglia (D'Esposito et al., 1995; Friedman & Miyake, 2017; Fuster, 2000; Hsu, Novick, & Jaeggi, 2014; Luna, Padmanabhan, & O'Hearn, 2010; Stocco et al., 2012). The executive function network in the brain shows considerable overlap across ages (Luna et al., 2010). Yet evidence suggests a developmental shift in anterior to more posterior activation with age: activation of middle and superior frontal, and of precentral gyri decrease with age (Velanova, Wheeler, & Luna, 2008).

Neurobiological evidence suggests that the adolescent brain may be especially sensitive to the hormonal effects of elevated stress (Lupien et al., 2009). Negative, stressful experiences affect performance and brain function associated with working memory (Noble et al., 2015; Richmond et al., 1967; Spielberg et al., 2015), sustained attention (Lim et al., 2016), and response inhibition (Carrion, Garrett, Menon, Weems, & Reiss, 2008; Elton et al., 2014; Jankowski et al., 2017; Lim et al., 2015; Mueller et al., 2012; Rahdar & Galván, 2014). High levels of stress culminate in declined intellectual ability and deteriorated academic performance (Pechtel & Pizzagalli, 2011). The investigation of exposure to violence and differences in brain function may shed light on the underlying mechanisms of disintegration of executive functions associated with exposure to high levels of stress.

The effects of early-life stress on cognition and development are well understood (Pollak, 2015; Shonkoff et al., 2012); yet less is known about these effects on adolescence (Romeo & McEven, 2006) which, again, is notably a period of high vulnerability to the environment (Eiland & Romeo, 2013; Luna, Paulsen, Padmanabhan, & Geier, 2013) and low self-control (Shonkoff et al., 2000; Steinberg, 2008). Exposure to violence may critically affect the development of

adolescent executive functions. Health and education investments in the violent and high NEET youth region of LAC may be better targeted by assessing neurocognitive evidence of environmental effects associated with alterations in brain development and function. We hypothesized there would be a significant association among more exposure to violence and differences in brain activation in the frontoparietal network of brain regions found to be activated in fMRI studies of executive functions.

METHODS

Five elementary schools participated in the study following a citywide invitation by the State Department of Education. Participants were invited in school meetings with all parents and guardians of preadolescents regularly enrolled in the 4th and 5th grades, the last two years of the first stage of elementary school in Brazil. The invites reached an estimated 500 families and we handed out informed consent forms to approximately 300 families who attended the meetings; parents or guardians who consented participation of their children later returned the informed consent forms in a sealed, anonymous envelope provided with the form. In total, 142 parents or guardians consented participation of their children in the study. The study was approved by the ethics committee of the Pontifical Catholic University of Rio Grande do Sul; Certificate of Evaluation of Ethics *CAAE* 57741516.6.0000.5336.

The study was divided in two stages. The first stage involved evaluations at the school, and the second, evaluations and brain scanning sessions at the Brain Institute. We sought all 142 preadolescents whose parents or guardians had consented participation and were able to scan 52 participants. Participants were excluded after the first stage of tests due to (1) IQ score below 75 (7 participants), (2) voluntary withdrawal from the investigation, by the guardian or participant (43 participants); (3) illiteracy or inability to fill out the questionnaires and tests (10 participants); and (4) frequent absence from school during visits for application of the tests and questionnaires (at least two additional attempts at data collection at the school were made if the participant missed school on the first visit) (5 participants). The loss of the remaining 25 participants was due to later voluntary withdrawal from the study, after completion of the first

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stage. These voluntary withdrawals reflected the unavailability to find a guardian to accompany the minor to the Brain Institute. The second stage involved participating in brain imaging scans and filling out additional tests and questionnaires; 52 participants completed participation in the study. The present paper reports the results for 42 right-handed preadolescents (boys: n = 27; girls: n = 15). Nine participants were excluded due to excessive head motion (see below). One participant was excluded due to focal demyelination on the left hemisphere temporal lobe. (A neuroradiological reading of the structural scans was carried out to ensure there were no lesions, malformations or other abnormalities in the brain). The average age of the 42 participants was 11.45 years (SD = 1.01).

Materials and procedures

The first stage in-school evaluations included I.Q. tests and filling out questionnaires on self-reported exposure to violence. IQ was investigated using the Wechsler Abbreviated Scale of Intelligence™ (mean = 95.27; SD = 10.69; range 75-114). Exposure to violence was investigated using the Juvenile Victimization Questionnaire (JVQ-R2) (Finkelhor, Ormrod, Turner, & Hamby, 2005). Evaluations included investigation of socioeconomic status, investigation of exposure to violence (JVQ-R2 full format), and an assessment of child behavior. Socioeconomic status (SES) was investigated using a standardized questionnaire for SES classification in Brazil (ABEP, 2016), which provides a score based on schooling and possession of consumer goods. The scores allow for categorization of SES from A (highest) to D (lowest) and subcategories in between. The average SES score corresponded to level C1 SES in Brazil (the range of scores was from D lower SES to B1 higher SES). Participation in the study occurred voluntarily and at no cost to participants. We provided participants and parents or guardians transportation and after completion of the study the neuroradiological reading and the IQ test report.

Exposure to violence: the Juvenile Victimization Questionnaire 2nd revision (JVQ-R2)

The JVQ-R2 is an instrument for evaluating self-reported interpersonal victimization in children and adolescents (Finkelhor et al., 2005). The JVQ-R2 gathers information on 34 items of specific forms of victimization, distributed in 5 modules: 9 items for Conventional Crime, 4 items for

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Maltreatment, 6 items for Peer and Sibling Victimization, 7 items for Sexual Victimization, and 8 items for Witnessing and Indirect Victimization. It also allows for evaluation of more recent victimization (last year-LY) and more chronic exposure to violence (lifetime-LT). Assuming the Item-level Scores proposed by the manual[2] for each item the reported presence of victimization is scored as 1, the absence is scored as zero; the sum of these scores makes up the total score. The JVQ-R2 can also be used to assess individual module scores. Each module can be scored to produce a LY or LT rate for, for example, Conventional Crime, or other type of victimization. Thus, a "yes" or 1 for the Conventional Crime module indicates that at least one report of exposure to Conventional Crime occurred, whereas a "no" or zero indicates no report of exposure to the type of victimization in that module.

The JVQ-R2 full interview was translated and adapted to Portuguese with the permission of its authors. In the present study, the JVQ-R2 was filled out in two separate occasions. The first occasion was at the schools. Participants filled out the reduced format of the questionnaire in groups of 10 to 20 individuals (i.e., the module that assesses the dichotomous presence/absence of types and instances of victimization only). The questionnaires were later scored and evaluated. Subsequently, a trained member of the clinical research team administered the full format of the questionnaire in an individual interview, in the second stage of the study. The full format of the JVQ-R2 gathers additional information about each of the types and instances of victimization reported in the reduced format.

Child Behavior Checklist for ages 6 to 18 (CBCL/6-18)

Behavioral and mental health problems were assessed using the Child Behavior Checklist for ages 6-18 (CBCL/6-18) and adapted for the Brazilian context (Bordin, Mari, & Caeiro, 1995). The CBCL/6-18 is a psychological assessment questionnaire (Achenbach & Rescorla, 2001) used for screening of child and adolescent mental health. It is filled out by parents or guardians, and it has been adapted for the Brazilian context (Bordin et al., 1995). The questionnaire consists of 138 items: 20 assess social competence and 118 assess behavior problems. The checklist

[2] http://www.unh.edu/ccrc/jvq/scoring.html

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includes 11 subscales that evaluate symptoms of internalizing problems (withdrawn, somatic complaints, and anxiety/depressed behaviors) and externalizing problems (delinquent and aggressive behaviors), as well as total problem scores (includes externalizing, internalizing, social, school, thought, and attention problems) (Achenbach & Edelbrock, 1991).

We analyzed CBCL/6-18 scores for the three broad-spectrum scales: internalizing and externalizing problems and total problem scores. The data was analyzed using the Assessment Data Manager (ADM) software (ASEBA, Burlington, Vermont) to assess raw scores and generate clinical, nonclinical, and borderline clinical profiles (Achenbach & Rescorla, 2001). The CBCL/6-18 scales in the present study showed good internal consistency reliability (Cronbach's alpha estimated in 0.801). The internal consistency (Cronbach's alpha) was also calculated for each broad-spectrum scale: internalizing problems ($\alpha = 0.760$), externalizing problems ($\alpha = 0.527$), and total problems ($\alpha = 0.729$).

fMRI design: Change Task

Functional Magnetic Resonance (fMRI) studies have utilized different tasks to investigate executive functions (Bremner et al., 2004; Thomaes et al., 2012), such as Stop tasks (Cai, Cannistraci, Gore, & Leung, 2014; Elton et al., 2014; Levy & Wagner, 2011; McNab et al., 2008; Meyer & Bucci, 2016; Mueller et al., 2010), Go/NoGo tasks (Gilman et al., 2018; Mazzola-Pomietto, Kaladjian, Azorin, Anton, & Jeanningros, 2009; Menon, Adleman, White, Glover, & Reiss, 2001) and the Change Task (Jha et al., 2015; Mueller et al., 2010; Nelson et al., 2007; Thomas et al., 2011). In the present study, we investigated brain function associated with a variant of the Go/NoGo and Stop tasks, called the Change task. The Change task is an event-related task adapted from previous studies (Nelson et al., 2007) in which participants must inhibit a prepotent response and replace it with a novel one. Correct responses involve inhibition of the more frequent, prepotent left-hand button press and execution of a right-hand button press. The task taps into sustained attention and response inhibition abilities (Boecker et al., 2011; Boecker, Gauggel, & Drueke, 2013; Logan & Burkell, 1986; Thomas et al., 2011).

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The Change task is an event-related task adapted from previous studies (Nelson et al., 2007). It consists in Go trials and Change trials. Go trials consist of visual presentation of either an X or an O, to which participants have to press buttons with their left middle and index fingers, respectively. Go trials made up 66% of the trials. Change trials consist of the presentation of a blue square, to which participants had to press a button with their right index finger; they made up 33% of the experiment. Since Go trials were more frequent, the task tests the ability of the participant to inhibit the prepotent response (Go - left middle and index fingers) and change it to a different, less frequent response (Change - right index finger).

The task lasted 8 min and 3 seconds and included 167 trials, 112 Go and 55 Change. Each trial began with a 500 ms fixation cross at the center of the screen, which was followed by the stimuli (presented for 1000 ms). The order of the presentation of the stimuli was randomized once, and each participant was presented with the same order. Stimulus presentation was offset by jittered intervals, which ranged from 0.75 to 2 sec (in 0.25 sec intervals) and were randomly inserted after each trial. A 6-sec dummy scan was inserted at the beginning of the task to ensure T1 magnetization reached an equilibrium state. An additional 10-sec rest was inserted at the end of the task. Response times and accuracy were recorded and computed for all trials using an MRI-safe buttonbox; stimulus was presented using E-Prime (Psychology Software Tools). Prior to the scanning session participants were given an out-of-scanner practice in an MRI simulator (Psychology Software Tools, Pittsburgh, PA). The goal was to help participants become acclimated with the scanner environment and noise. The practice session included a shorter version of the task.

Data collection

fMRI parameters

Data was collected on a GE HDxT 3.0T MRI scanner with an 8-channel head coil. Three MRI sequences were acquired: a T1 structural scan (TR/TE = 6.16/2.18 ms, isotropic 1 mm^3 voxels); two task-related functional FMRI EPI sequences (run 1 = 8 min; run 2 = 8 min 04 s). For the task EPI sequence we used the following parameters: TR = 2000 ms, TE = 30 ms, 29 interleaved

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slices, slice thickness = 3.6 mm; slice gap = 0.3 mm; matrix size = 64 x 64, FOV = 220 x 220 mm, voxel size = 3.75 x 3.75 x 3.90 mm. During the scan, real-time motion detection software was used to monitor participant cooperation. In case participants presented more than 0.9 mm of motion in more than 20 TRs before completing the run, we interrupted the experiment and ran the task again. We made one attempt to re-run the task if it was stopped due to excessive head motion.

fMRI analyses

Functional data were processed using AFNI's (http://afni.nimh.nih.gov/) afni_proc.py program (Cox, 1996). Preprocessing included slice-time and motion correction, smoothing with a 6mm FWHM Gaussian kernel, and a non-linear spatial normalization to 3.5 x 3.5 x 3.5 mm voxel template (HaskinsPedsNL template) (Molfese, Glen, Mesite, Pugh, & Cox, 2015). Time points between volumes with motion greater than 0.9mm were censored from the data. Nine participants who finished the scanning session were excluded due to excessive motion. The criterion for exclusion due to head motion was: excessive motion in 20 % of the TRs. The average head motion for the participants included in the study was mean = 0.1262 (SD = 0.065).

First level analysis included modeling regressors for each condition, Change and Go, convolved with the canonical hemodynamic response function as implemented in AFNI (Cox, 1996). To correct for multiple comparisons, the 3dClustSim program using the autocorrelation function blurring estimates and performing 10,000 Monte Carlo simulations was used to calculate the cluster threshold for a corrected p-score of $\alpha < 0.05$. Results showed that the threshold of $p < 0.005$ combined with a minimum cluster size of 71 voxels (3,038.8 µl) corresponded to a corrected score of $\alpha < 0.05$.

Correlations: fMRI, exposure to violence, and behavior

We carried out correlations among the JVQ-R2 scores and the images collapsed across Change and Go trials. We collapsed across conditions to investigate the brain activation associated with the duration of the task. The correlation was calculated using the 3dRegAna function from the

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AFNI package (Cox, 1996). We report results that survived the corrected threshold of $p < 0.005$ and a minimum of 71 voxels. The correlation was carried out with the *Lifetime* and the *Last Year* (LY) scores for JVQ-R2 to investigate the effects of longer (chronic) exposure and more recent exposure to violence, respectively. We carried out separate analyses of correlations for each JVQ-R2 module to investigate the effects of each type of violence on brain function. We included the age, IQ, and SES of participants as covariables in the analyses to control for their effects.

Betas

The average betas for functional regions of interest were extracted for individual participants for the regions that negatively correlated with the JVQ-R2 scores. These betas were subsequently correlated with the JVQ-R2 scores for the participants.

Behavioral data analysis

Participants responded to the task using mice buttons. The response and response times were recorded using E-Prime (Psychology Software Tools, Pittsburgh, PA) for all trials. Behavioral data was analyzed using Spearman's rho correlation for significant association between response times (RT) and accuracy (ACC) on the task and the JVQ scores. To test if the length of the task would have an effect on the participants' performances, we correlated the mean ACC and RT of each trial with the order of the presentation of the trials. To test for the effects of chronic stress on the performance over time, we correlated (Pearson's correlation) each participant's RT and ACC for each trial with the order of presentation of each trial in the experiment. We then correlated the resultant *r* for each participant with the JVQ scores. We also calculated a delta for the response time in the experiment. The increase in latency was calculated making a correlation among the response times for all items (Go and Change) and the item presentation number (e.g. the first item is 1, the second, 2, and so on). The resulting *r* value was used as an index of the latency: a negative r represented a decrease in response time with time, and a positive r, an increase with time.

RESULTS

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fMRI Results

Brain function and exposure to violence

Results show that more exposure to violence was associated with less activation of anterior and posterior clusters of brain regions; these brain regions are among the brain circuitry associated with executive functions in the literature. More chronic violence was associated with less activation of an anterior cluster of brain regions that includes the anterior cingulate gyrus, the middle and superior frontal gyri, the precentral gyrus, and the insular cortex. More recent exposure to violence was associated with anterior and posterior clusters of less activation that included anterior cingulate, precentral, superior frontal gyri and posterior cingulate gyrus and posterior parietal lobe (Figure 1; Table 1).

FIGURE 1 and TABLE 1 ABOUT HERE

Brain function and behavior

The results suggest an overlap of less activation in anterior cingulate and superior frontal regions for JVQ-R2 life time and last year. Only the JVQ-R2 last year scores showed a significant correlation with a posterior cluster of regions, which include the left superior parietal lobe. Figure 2 shows a rendering of the overlapping activation in anterior cingulate and superior frontal regions.

FIGURE 02 ABOUT HERE

The results also show that an increase in latency in response time was associated with less activation of the anterior and posterior clusters identified. Beta values extracted from the clusters negatively correlated with an increase in the response time over the experiment (a response time delta). Figure 3 shows the scatter plots for the beta values and the increase in response time (latency) [Spearman 1-tailed correlations: DELTA RT x L INSULA = - 0.381 ($p<0.05$); DELTA RT x POSTERIOR= - 0.286 ($p=0.046$); DELTA RT x ANTERIOR = -0.409 ($p<0.01$)].

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FIGURE 3 ABOUT HERE

Behavioral Results

The mean accuracy (ACC) for the whole group was 0.83 (SD = 0.13) and mean response time (RT) was 636.7 (SD = 58.7). For the *Change* trials, mean ACC was 0.88 (SD = 0.09) and mean RT was 625.44 (SD = 64.32). For the *go* trials, mean ACC was 0.80 (SD = 0.17) and mean RT was 642.49 (SD = 60.79). There were no significant correlations among RT and the JVQ scores (p=0.341) or and the CBCL Scales (p = 0.376 for Internalizing Behaviors, p=0.283 for Externalizing Behaviors, and p=0.477 for Total Problems Scale). There were no significant correlations among ACC and JVQ (p=0.352) or CBLC (p=0.308 for Internalizing Behaviors, p=0.197 for Externalizing Behaviors, and p=0.356 for Total Problems Scale). The mean accuracy for all participants decreased over the experiment ($p < 0.001$), as the response time increased ($p < 0.01$). The correlation of JVQ scores and the decrease in performance (RT or ACC) was not significant (p = 0.121 for RT, and p = 0.415 for ACC).

Exposure to Violence: Juvenile Victimization Questionnaire

The majority of preadolescents (36 participants, 85.7%) had experienced at least one form of victimization over the life span, and 31 (73.8%) reported being exposed to violence over the last year. The most common type of violence exposure was conventional crime (69%), followed by witnessing/indirect forms of violence (59.5%). Spearman's *rho* correlation showed a significant negative correlation among the JVQ Modules 1 (Conventional Crime) and 2 (Maltreatment) with the CBCL Total Social Competence Score (p = 0.019 and p = 0.024, respectively). The Social Competence Score assesses social interaction patterns; for instance, if the respondent interacts well with other preadolescents and family members, how many close friends they have, how often they meet with the close friends, and what is their level of independency for playing or working (Bordin et al., 2013). The correlation between low scores for Social Competence and high scores for exposure to violence suggest an association between the increased exposure to violence and diminished ability to socialize with peers and family. Table 2 shows descriptive statistics (mean ± SD) for each domain module of JVQ-R2 full interview, as well as for the total score. Studies have shown JVQ-R2 scores correlated with hair cortisol concentrations, thus

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suggesting self-reported scores provide a reliable index of more stressful experiences (Buchweitz et al., 2019; Grassi-Oliveira et al., 2012)

TABLE 2 ABOUT HERE

Internalizing and externalizing behaviors: the Child Behavior Checklist

The analyses of CBCL/6-18 scores included 42 preadolescents (boys: *n* = 26; girls: *n* = 16). The results show that 64.3 % (*n* = 27) of the sample scores for internalizing behaviors were at the clinical level (borderline level: 4.7 %; nonclinical level: 31.0 %), and 66.7 % (*n* = 28) of the sample scores for externalizing behaviors were at the clinical level (borderline level: 9.5 %; nonclinical level: 23.8 %). The total problems scores were 61.9 % (*n* = 26) at the clinical level (borderline level: 11.9 %; nonclinical level: 26.2 %). We investigated sex-specific effects and found no significant sex differences on CBCL/6-18 scores for the different symptoms: withdrawn (*t* = - 0.726; *P* = 0.472), somatic complaints (*t* = - 0.070; *P* = 0.944), anxiety/depression (*t* = - 0.443; *P* = 0.660), rule-breaking behavior (*t* = 1.002; *P* = 0.322), aggressive behavior (*t* = - 0.099; *P* = 0.922), internalizing problems (*t* = - 0.435; *P* = 0.666), externalizing problems (*t* = 0.211; *P* = 0.834), and total problems (*t* = 0.372; *P* = 0.712).

DISCUSSION

The present study shows that more exposure to violence was associated with less activation of anterior and posterior brain regions in an inhibitory control task, in Latin-American preadolescents. They also show that a deterioration in the performance (increase in latency of response) was associated with less activation of these anterior and posterior brain network. Few studies have investigated inhibitory control in preadolescents exposed to violence or other forms of stress; to our knowledge, there are no brain imaging studies of Latin-American adolescents that investigate exposure to violence and executive functions in the brain. Our results are in line with the literature on the association among trauma, violence, institutionalization and other negative life events with brain function. Studies show hyperactivation of the inferior frontal gyrus, anterior cingulate cortex, precentral and

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postcentral gyri, insula, caudate, and putamen in children who experienced deprivation in institutionalized care (Mueller et al., 2010); and hypoactivation of middle and medial frontal gyri, inferior temporal lobe, and hyperactivation of insular cortex and occipital lobe were identified in maltreated adolescents with PTSD (Carrion, Garrett, Menon, Weems, & Reiss, 2008). Severely abused children showed reduced activation in the ventral and dorsal frontal attention regions of left inferior frontal cortex, anterior insula and dorsolateral-prefrontal cortex (Lim et al., 2016). Studies show altered hyper and hypo activation associated with negative experiences; the direction of differences is not always the same. But one pattern is clear: there is atypical recruitment of cortical areas of the brain that underpin executive functions in preadolescents exposed to violence. We show a dimensional effect of exposure to violence and evidence of atypical recruitment of anterior and posterior network of areas in victimized preadolescents during response inhibition.

Chronic exposure to violence (life time) was associated with less activation of an anterior cluster. In contrast, more recent exposure (last year) was associated with less activation in the anterior and posterior cingulate cortex and in the posterior parietal lobe. The posterior parietal cluster was identified only in association with more recent violence. These regions are also associated with cognitive control, behavioral flexibility, emotional regulation and working memory (Radley et al., 2015). We underscore that age, intelligence and socioeconomic status were included as covariables in the investigation. These variables have been associated with differences in brain function and structure (Kim et al., 2013; Luna et al., 2010; Noble et al., 2015; Piccolo, Merz, He, Sowell, & Noble, 2016)

The literature shows different results for accuracy and response time in the Change task. Untreated bipolar adolescents showed significantly lower accuracy in Change trials than the control group (Nelson et al., 2007), but most studies found no group differences in task accuracy (Kim et al, 2012; Roberts and Husain, 2015; Bruce et al., 2013; Mueller et al, 2010; Jankowski et al, 2017). Compared to controls, response time was greater in a patient with pre-SMA lesion (Roberts and Husain, 2015) and in maltreated adolescents (Mueller et al, 2010),

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however significant difference in RT has not been identified (Kim et al, 2012; Nelson, et al, 2017; Jankowski et al, 2017).

Chronic exposure to violence during childhood is associated with an increased risk for a broad range of developmental difficulties, including behavioral, emotional, and learning problems (Bick & Nelson, 2016; Moffitt & Tank, 2013; Tsavoussis, Stawicki, Stoicea, & Papadimos, 2014). Chronic exposure to violence is also associated with risk for psychosis, ADHD (Attention Deficit and Hyperactivity Disorder), depression, anxiety among other impairing conditions (Fonzo et al., 2016; Lupien et al., 2009; Banny, Cicchetti, Rogosch, Oshri, & Crick, 2013). The deactivation of bilateral networks associated with inhibitory control and sustained attention suggests a deleterious effect of exposure to violence on brain function associated with an ability that is associated with quality of life. Inhibitory control involves the ability to control one's attention, behavior, thoughts, and/or emotions to prevail over impulses and habits of thoughts or actions in order to select a more appropriate behavior consistent with the completion of goals (Boecker et al., 2013; Diamond, 2013; Hughes, 2013). It is involved in decision-making processes, deciding not to eat a cake in order to keep with one's dietary plan, or to stay home and finish an academic work instead of going out to party (Aron, 2011). Inhibitory control is associated with interconnected processes that allow preadolescents to focus on their homework despite a desire to play, or despite of the lack of a safe place to study at home (Zhang, Hughes, & Rowe, 2012).

The insular cortex is a complex and multipurpose structure, underpinning numerous cognitive functions related to perception, emotion, and interpersonal experience (Gasquoine, 2014; Uddin et al., 2017). The insula is involved with general attention processes (Menon & Uddin, 2010; Posner, Rothbart, & Voelker, 2016; Seeley et al., 2007). Lesions to the the left insula have been associated with detriments in cognitive flexibility in a set-shifting task (Varjačić et al., 2017). It is postulated that after detection of the salient stimulus, the anterior insula enables the suppression of the default mode network and initiates the attention shift to engage cognitive and task control systems (Namkung, Kim, & Sawa, 2017; Sridharan, Levitin, & Menon,

2008). Insular malfunction may play a role in the origin of psychosis in schizophrenia (Kapur, 2003; Palaniyappan & Liddle, 2012). Adults with history of child maltreatment show reduced connectivity among insular and limbic structures (van der Werff et al., 2012). Resiliency, conversely, was associated with increased connectivity within the saliency network (Van der Werff et al., 2013).

The disengagement of the anterior regions of the brain, such as the insular cortex might imply deterioration in function along the saliency network. Studies show preadolescents and children exposed to abuse showed reduced activation in the insula and attention-related regions such as the dorsolateral prefrontal cortex, during a sustained attention task (Lim et al., 2016). The exposure to childhood stress was also associated with reduced insular activation along saliency network structures (Birn et al., 2017). The brain imaging evidence thus suggests that exposure to adverse, negative experiences by children and adolescents may be associated with alterations in insular cortex function. Public policymaking and agencies may benefit from understanding the neurocognitive effects of exposure to violence and focus on executive function training; for example, studies have shown benefits and transfer of executive functions training (Jaeggi, Buschkuehl, Jonides, & Shah, 2011; Salminen, Strobach, & Schubert, 2012)

It remains to be understood if less activation of the frontal and posterior networks are associated with a maladaptive mechanism. Are preadolescent's brains "shutting down" due to a lifetime of exposure to violence? Are preadolescent's brains overloaded with filtering and focusing attention to survive? The present study cannot answer these questions, but the results do suggest that there may be a maladaptive coping mechanism of the brain taking hold. If brain function associated with the ability to control inhibition and sustain attention is severely impaired by exposure to violence, one can only begin to speculate the school and social-life effects that may follow, such as impaired learning and studying abilities, impaired social abilities, and poor impulse control.

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[1] http://www.unh.edu/ccrc/jvq/scoring.html

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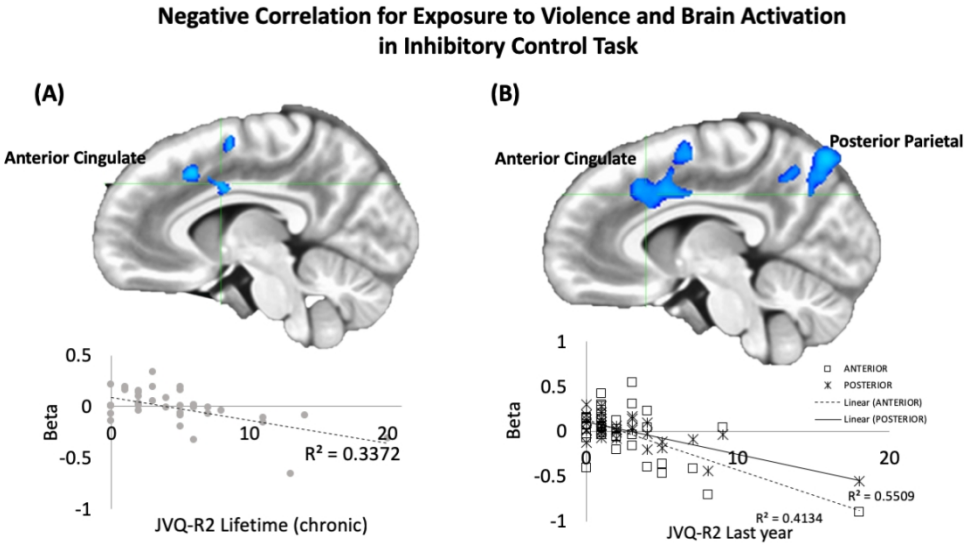

Figure 01. Negative correlation among JVQ-R2 LT (Chronic Violence) and LY (Recent Violence) scores with activation for all conditions (Go and Change) in the Change task. Clusters significant at $p < 0.05$ corrected for multiple comparisons (71 voxel threshold and $p < 0.005$). (A) Sagittal slice showing anterior cingulate cluster of negative corrrelation with LT scores and the respective dispersion plots for the JVQ scores and the beta values for the whole cluster (crosshair at x=-6, y=3, z=35). (B) Sagittal slice showing anterior cingulate and posterior parietal clusters of negative correlation with LY scores and the respective dispersion plots for the JVQ scores and the beta values for the whole cluster (crosshair at x=-6, y=19, z=35). AFNI (Cox, 1996).

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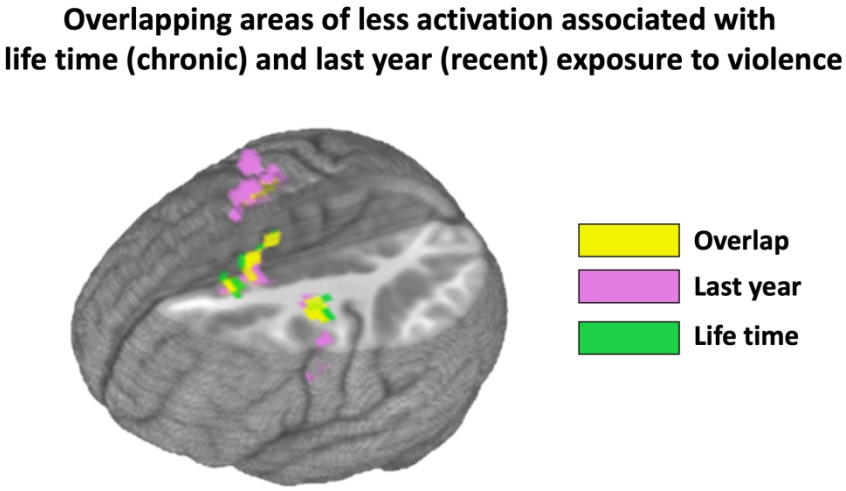

Figure 02. Overlap among the clusters of anterior cingulate negative correlation with life time and last year exposure to violence. Yellow represents overlapping areas; violet represents last year, and gree, life time. AFNI (Cox, 1996).

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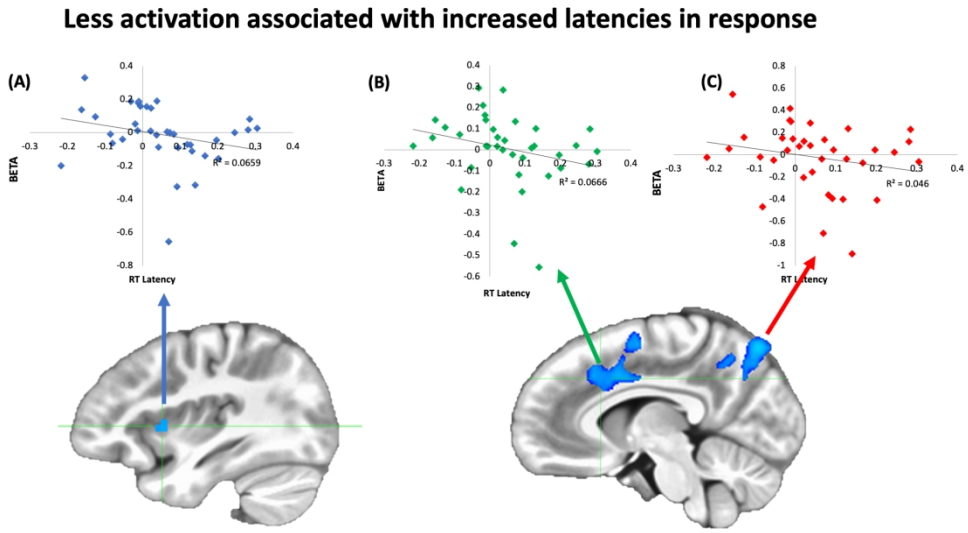

Figure 3. Association among increase in latency in response times and activation (betas) for the clusters of negative correlation with exposure to violence. Participants who reported more exposure had increased latencies in response as the experiment progressed. (A) Dispersion plot for the insular cortex cluster in association with life time (LT) exposure. (B) Dispersion plot for the anterior cingulate cluster in association with last year (LY) exposure. (C) Dispersion plot for the posterior parietal cluster in association with last year (LY) exposure. Betas were extracted for the whole clusters. Latency represents the increase in latency during the experiment.

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Region (atlas number)	Voxels	Peak		
JVQ-R2 Life Time (chronic)		**x**	**y**	**z**
Right-Hemisphere				
Anterior Cingulate (caudal) (75)	3	3	6	39
Precentral (96)	2	47	2	38
Superior Frontal (66)	30	9	-1	55
Left-Hemisphere				
Anterior Cingulate (caudal) (41)	11	-8	2	32
Middle Frontal (42)	45	-28	-5	37
Pars Opercularis (56)	62	-45	4	12
Precentral (62)	33	-45	3	34
Superior Frontal (66)	52	-23	-8	55
Insula (73)	9	-35	5	4
JVQ-R2 Last Year				
Right-Hemisphere		x	y	z
Anterior Cingulate (caudal) (75)	4	4	2	40
Middle Frontal (76)	13	29	-3	40
Postcentral (94)	1	35	-16	40
Posterior Cingulate (95)	1	10	-54	14
Precentral (96)	64	34	-12	40
Superior Frontal (100)	54	15	1	62
Left-Hemisphere				
Anterior Cingulate (caudal) (41)	40	-7	7	36
Middle Frontal (caudal) (42)	45	-3	8	36
Cuneus (43)	9	-14	-76	30
Precentral (62)	25	-52	4	29
Precuneus (63)	61	-10	-65	34
Superior Frontal (66)	71	-4	5	45
Superior Parietal (67)	11	-15	-65	51

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Participants, Exposure to Violence and Types of Exposure					
	n	%	Min	Max	Mean (SD)
Lifetime	36	85.7	1	20	5.25 (4.18)
Conventional crime	29	69	1	7	2.55 (1.52)
Maltreatment	13	31	1	2	1.23 (0.44)
Peer and sibling victimization	14	33.3	1	4	1.71 (1.21)
Sexual victimization	04	9.5	1	2	1.25 (0.5)
Witnessing and other exposure	25	59.5	1	5	2.64 (1.44)
Last Year	31	73.8	1	18	3.35 (3.51)

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