COGNITION, PLASTICITY, AND FUNCTIONING AFTER CHILDHOOD ADVERSITY IN MAJOR DEPRESSIVE DISORDER

by

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Abstract

Background: There is a compelling association between childhood adversity and Major Depressive Disorder (MDD) in adulthood, including more severe and treatment-resistant presentations of illness. Childhood adversity is also related to deficits in neurocognition, smaller hippocampal volume, and changes in structural and functional brain connectivity. At the same time, neurocognitive impairment accompanies many cases of MDD, but the extent to which childhood adversity accounts for cognitive variance has not been investigated. Furthermore, it is unclear whether adversity is related to plasticity, indicated by response to neurocognitive treatment, and if the relationship between cognition and functioning differs among individuals based on their history of childhood adversity. ***Objective:*** The current research sought to clarify how early adversity and select characteristics of illness relate to cognitive differences in MDD, as well as response to Cognitive Remediation (CR), a treatment that promotes neurogenesis and plasticity through cognitive exercise and compensatory strategies. In addition, this project examined the moderating role of adversity in the relationship between cognition and skills required for everyday functioning. ***Method:*** Thirty-nine individuals with MDD who previously completed a 10-week CR intervention, as well as neurocognitive and functional skills testing, were re-recruited to engage in a retrospective interview on childhood adversity. ***Results:*** More adversity endured as a child and repeated depressive episodes were associated with poorer cognition in adulthood, $\beta = -.45$, $t(36) = -3.34$, $p = .002$, and $\beta = -.33$, $t(36) = -2.53$, $p = .017$, together accounting for 37.4% of variance in cognition. Childhood adversity was associated with more improvement following CR, but this relationship was small in magnitude, $\Delta R^2 = .05$, $\Delta F(2, 36) = 4.36$, $p = .044$. A significant association between cognition and functional performance was apparent only among individuals who experienced high levels of adversity, $b = .63$, $SE =$

.25, p = .018. ***Conclusions:*** Our findings highlight childhood adversity and multiple depressive episodes as factors associated with cognitive impairment in MDD. We emphasize early trauma as an important variable to be addressed in neurocognitive treatment and research.

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List of Abbreviations

ABCR: Action-Based Cognitive Remediation

BDI: Beck Depression Inventory

BVMT: Brief Visuo-Spatial Memory Test-Revised

CECA: Childhood Experience of Care and Abuse Interview

CR: Cognitive Remediation

D-KEFS: Delis-Kaplan Executive Function System

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

HPA: Hypothalamus-Pituitary-Adrenal

HSREB: Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

HVLT: Hopkins Verbal Learning Test

MADRS: Montgomery-Åsberg Depression Rating Scale

MDD: Major Depressive Disorder (MDD)

M.I.N.I.: Mini-International Neuropsychiatric Interview

tCR: Traditional Cognitive Remediation

TMT-A: Trail Making Test A

TMT-B: Trails Making Test B

UPSA-B: Brief UCSD Performance-Based Skills Assessment

WRAT-3: Wide Range Achievement Test, 3rd Edition

Chapter 1

Introduction

Major Depressive Disorder

Major Depressive Disorder (MDD) is an impairing illness predominantly characterized by depressed mood and loss of pleasure. Individuals diagnosed with MDD experience a range of additional symptoms including changes in appetite or weight, slowing down or restlessness of movement and speech, difficulty sleeping, loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death or hurting oneself. A diagnosis is given when an individual experiences at least five symptoms, including depressed mood or anhedonia, during the majority of time for at least two weeks (American Psychiatric Association, 2013).

While a minimal duration of two weeks is specified by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), there is considerable variation in the length of time to remission, recurrence of episodes, and illness chronicity. In population-based studies, mean episode duration is between 13 and 30 weeks, and the majority of individuals recover within one year (Otte et al., 2016). At the same time, MDD recurs in about 40-50% of individuals after an initial episode, and the rate of recurrence is higher among those who have already endured repeated episodes (Monroe & Harkness, 2011; Gonzales, Lewinsohn, & Clarke, 1985). The median age of illness onset is around 25 years, with the greatest risk of onset ranging from adolescence to early 40s (Bromet et al., 2011). In addition to the strong probability of a repeated episode, antidepressant medication does not alleviate symptoms in as many as 50-60% cases (Otte et al., 2016).

In combination with the individual burden described above, MDD is the leading contributor to non-fatal health loss at a global level, quantified by the highest estimate of Years Lived with Disability worldwide (World Health Organization, 2017). The average 12-month prevalence of MDD is approximately 6%, with a lifetime prevalence above 18% (Bromet et al., 2011). The pernicious impact of depression continues beyond episode remission, as residual symptoms and psychosocial impairment often remain after the 'cloud' of a depressive episode has departed (Ormel, Oldehinkel, Nolen, & Vollebergh, 2004). Furthermore, depression impacts workplace productivity through decreased quality of performance and increased absenteeism, with annual productivity losses of over $9.3 billion USD in Canada alone (Evans-Lacko & Knapp, 2016). Evidently, the societal and personal cost of MDD necessitates dedicated efforts to refine treatment for the symptoms and far-reaching impairment associated with this disorder.

Cognitive Impairment and Neurophysiology in MDD

Cognitive impairment is a central feature of MDD that persists during active episodes and in states of remission (Rock, Roiser, Riedel, & Blackwell, 2014). Overall impairment is moderately severe, falling on average 0.5 to 1.0 standard deviation below the population mean (Bowie, Gupta, & Holshausen, 2013). Specific deficits are seen in executive function, memory, processing speed, and attention (Lam, Kennedy, McIntyre, & Khullar, 2014), and are associated with poor academic, occupational, and functional outcomes (Lee, Hermens, Porter, & Redoblado-Hodge, 2012).

Although cognitive impairment is recognized as a debilitating symptom of MDD estimated to occur in about two-thirds of depressed patients (Rock et al., 2014), there is considerable variability in the nature and magnitude of its manifestation. Current illness

severity is a major determinant of cognitive performance while in episode, but the total length of previous depressive episodes is more prominently associated with cognitive functioning in remission (Gorwood, Corruble, Falissard, & Goodwin, 2008). Furthermore, those with a younger age of illness onset, repeated episodes, and more severe residual symptoms show greater deficits (Burt, Zembar, & Niederehe, 1995; Basso & Bornstein, 1999; Williams et al., 2000). Demographic variables such as older age, lower education level, and unemployment are also independently associated with poorer cognition both in episode and during remission (Gorwood et al., 2008). Another study revealed that lower cognitive reserve often precedes depression and is associated with persistence and comorbidity (Koenen et al., 2009). Accordingly, it is possible that cognitive impairment in depression may be partly attributable to the fact that individuals with lower cognitive reserve are more inclined to develop MDD in the first place, including more persistent forms of the disorder and greater rates of co-occurring illnesses.

Neurologically, individuals with MDD show differences in structural and functional connectivity; altered neurotransmission and reduced plasticity underlie changes in networks responsible for cognitive control and affective processing (Otte et al., 2016). For instance, there is less connectivity in the dorsolateral prefrontal cortex, an integral region for many cognitive tasks including those that require goal-directed attention (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Hyperactivation of the amygdala, which mediates physiological and behavioural responses associated with fear and strong emotions, has also been found among individuals with MDD (McEwen, 2005). Additionally, meta-analyses have confirmed smaller hippocampal volumes in individuals with depression compared to healthy controls and patients diagnosed with other psychiatric disorders (for example, see Goodkind et al., 2015). While the

causal direction of the relationship between MDD and hippocampal size is unclear, previous studies identified more atrophy among individuals who experienced multiple episodes and longer durations of illness (Sheline, Sanghavi, Mintun, & Gado, 1999; Videbech & Ravnkilde, 2015). These researchers speculate that sustained depression has a toxic effect on the hippocampus, resulting in the reduction of tissue volume and associated memory impairment.

Functional Impairment in MDD

Individuals with MDD additionally experience substantial impairment in occupational, relational, and personal aspects of life, and mediational studies suggest that cognitive deficits account for the greatest percentage of variance in such dysfunction (McIntyre et al., 2013). For instance, seventy-nine percent of those with MDD reported interference with work functioning, defined as decreased work productivity and/or absenteeism (Gilmour, & Patten, 2007), and more than one-quarter of work loss was directly linked to difficulty with concentration, memory, understanding, and thinking clearly (Buist-Bouwman et al., 2008). In addition, cognitive impairment among individuals with MDD is also associated with limitations in activities of daily living, such as managing money, taking medications, shopping for groceries, and preparing meals (Xiang & An, 2015). Alarmingly, the aforementioned difficulties persist even after depressive symptoms subside (Bortolato, Carvalho, & McIntyre, 2014).

Although particular cognitive domains associated with functional impairment among individuals with MDD have not been sufficiently investigated, few studies on this topic suggest specific facilities that play a mediational role. One study reported that measures of attention, executive functioning, visuo-spatial processing, and learning were associated with disability across work, education, and residential domains 6 months following hospitalization for a major depressive episode (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Another study identified a

moderate relationship between psychomotor speed and limitations in physical activity, hobbies, and daily routines, as well as a moderate correlation between memory and the number of days an individual was unable to perform regular activities. These associations were apparent even after controlling for depression severity (Naismith, Longley, Scott, & Hickie, 2007).

In sum, while cognitive and functional impairment are experienced by many individuals with MDD, we do not fully understand the associated mechanisms and risk factors for experiencing these deficits. Previous work on neurocognition in depression recognizes variance explained by demographic factors as well as qualities of illness. In other psychopathology research, increasing attention is being directed towards understanding different expressions of illness based on etiological and unique phenotypic profiles (Insel et al., 2010; Hasler, Drevets, Manji, & Charney, 2004), but this approach has not yet been adopted to the same extent in research on neurocognition in MDD. We propose childhood adversity as a variable critically related to the expression of illness that may pose an individual at risk for impaired cognition. As part of our rationale, we draw from research that shows a strong association between childhood adversity and more severe and chronic psychopathology, as well as preliminary evidence suggesting that early adversity also has a toxic effect on neurocognitive functioning.

Childhood Adversity and Depression

Individuals with a history of childhood adversity have greater than a twofold risk of developing MDD (Heim & Binder, 2012), and among those who develop the disorder, have an earlier age of onset, more severe symptoms, and exhibit greater resistance to treatment compared to those who did not experience early trauma (Liu, 2017; Nanni, Uher, & Danese, 2012). There is a dose-response relationship such that greater number of childhood adversities are associated with a more severe and chronic depression (Chapman et al., 2004).

Childhood adversity in the current study encapsulates emotional, physical, and sexual abuse, as well as parental discord and bullying. Emotional abuse involves both caregiver antipathy and neglect. Antipathy can be in the form of criticism, hostility, or dislike towards the child and can also involve intentionally eliciting feelings of guilt, shame, or fear. Emotional neglect is when a child's fundamental emotional needs are not met, such as responding to them when in distress or providing adequate attention. Physical neglect may also be present and includes failure to meet basic physical needs like food, clean clothing, protection from harm, and provision of medical care. Physical abuse is violence directed against a child by any adult perpetrator, including parents, relatives, teachers, and other authority figures, and may be a single instance or occur over time. Sexual abuse involves any age-inappropriate sexual activity and abuse of a perpetrator's power over a child. This includes sexual activity between children and adult family, friends, or authority figures, and can range from sexualized kissing to touching and full intercourse. Verbal and physical arguments between parents, as well as climates of tension and hostility are encapsulated in parental discord. Finally, bullying includes physical attacks as well as verbal teasing and threats from same-age peers.

It is difficult to estimate the prevalence of childhood adversity in the general population due to different ways of operationalizing abuse and varying incidence rates across maltreatment categories. A systematic review of studies using self-reported maltreatment found that in North America, the median prevalence rates of sexual and physical abuse were 20.4% and 12.0%, respectively. Prevalence of emotional abuse ranged from 13.8% for boys to 28.4% for girls, and a median rate of 16.6% of boys experienced neglect compared to 40.5% of girls (Moody, Cannings-John, Hood, Kemp, & Robling, 2018). A study that assessed physical abuse, sexual abuse, and exposure to intimate partner violence among a nationally representative Canadian

sample revealed an overall prevalence of 32%, with a range of 8% to 26% across individual types. This project also highlighted a dose-response relationship between more types of abuse experienced and greater odds of experiencing mental illness (Afifi et al., 2014).

There is also evidence to suggest that chronicity of depression is associated with a higher prevalence of childhood trauma, and especially those who experienced multiple forms and incidents (Wiersma et al., 2009). At the same time, not everyone who experiences severe adversity will suffer from clinical depression. A recent population-based study found a range of 50-100% of individuals who did not show clinically significant levels of depression or anxiety following severe adversity, depending on the type of maltreatment endured (Rehan, Antfolk, Johansson, Jern, & Santtila, 2017). Nonetheless, the prevalence of childhood abuse is markedly higher in samples with MDD, and experience of maltreatment in one or more domain accounts for 54% of the population attributable risk fraction for depression (Anda et al., 2002). A host of neurophysiological changes related to the stress of childhood adversity provide some explanation for why trauma is such a potent risk factor for developing MDD.

Neurophysiology of Childhood Adversity

Neurological mechanisms involved in the adaptation to stressful life events in adulthood are often compromised as a result of early trauma, and in turn give rise to neurophysiological patterns seen in depression. The hypothalamus-pituitary-adrenal (HPA) axis is a primary system involved in the stress response, activated in the face of threat and de-activated when danger is no longer present (McEwen, Gray, & Nasca, 2015). The HPA axis is especially labile in childhood and adolescence; experiences of severe stress during this period are associated with the extent and length of its activation to everyday perturbations as well as to additional stressors encountered in adulthood (Lupien et al., 2009; Albers, Riksen-Walraven, Sweep, &

Weerth, 2008; Perlman, Webster, Herman, Kleinman, & Weickert, 2007). Childhood trauma is associated with over-sensitivity of the stress response, neuroendocrine changes, and compromised neural circuitry required for emotional and autonomic control. These processes underlie clinical symptoms of depression and also have implications for neurocognition (Heim, Newport, Mletzko, Miller, & Nemeroff, 2007).

Neurocognition After Childhood Adversity

Cognitive deficits appear to coincide with alterations in brain architecture provoked by severe stress. Stressful experiences alter the size and functional connectivity of the amygdala, hippocampus, and prefrontal cortex – all implicated in depression and essential for learning, memory, and executive functioning (Shonkoff et al., 2012). For example, exposure to chronic stress hinders neurogenesis in the hippocampus, which manifests through problems in the development of linguistic, cognitive, and social-emotional skills (McEwen & Gianaros, 2011). Furthermore, elevated cortisol causes changes in neural connectivity within the prefrontal cortex, hampering its ability to regulate amygdala activity and the tenacity of executive functions such as decision-making, self-regulation, and impulse control (Boyce & Ellis, 2005).

Correspondingly, there is initial evidence from human studies to suggest that children who have been abused or neglected exhibit deficits in memory, executive skills, processing speed, and emotional functioning as they mature (Majer, Nater, Lin, Capuron, & Reeves, 2010; Gould et al., 2012). Among individuals with no psychiatric diagnosis, Majer et al. (2010) found that emotional abuse and physical neglect were associated with impaired working memory performance, and that individuals who experienced physical neglect also exhibited deficits in long-term memory. Work by Gould et al. (2013) demonstrated relative deficits in visual memory, executive functioning, processing speed, and emotional processing among individuals

with self-reported history of emotional and physical abuse and neglect (including healthy participants and individuals with MDD in their sample).

Evidently, there are a breadth of neurological pathologies identified among adults who experienced childhood maltreatment. The aforementioned work identified cognitive impairment among healthy individuals who endured childhood abuse and neglect (Majer et al., 2010); however, these individuals did not experience severe forms of abuse as is more common among those who develop psychiatric illness, and therefore the full extent of consequences associated with early trauma may not have been captured. Gould et al. (2013) included both healthy and depressed individuals and found select limitations in cognition that were associated with childhood adversity, but was privy to subjective interpretations of adversity through the use of self-report measures. In addition, they did not include individuals with MDD who had not experienced adversity and therefore were not able to assess the independent impact of illness on cognition. The current study addresses these limitations by investigating cognition of individuals experiencing clinical depression who suffered a range of adverse experiences, employing a semi-structured interview shown to reliably and objectively assess retrospective accounts of early adversity.

Functional Competence After Childhood Adversity

While preliminary evidence indicates an association between early-life trauma and impairment in executive functioning, hippocampal-dependent memory, and psychomotor processing speed (Majer et al., 2010; Gould et al., 2013), no previous research has examined the relationship of early adversity and functional competence in adulthood. Interestingly, the domains that may be most implicated following adversity appear to align with the cognitive facilities identified as mediators of functional outcomes as previously described, although

empirical validation is needed to support this observation. The current project seeks to answer the question of whether early adversity is associated with functional competency, and to identify if the cognitive profile associated with early trauma is especially consequential for skills needed in everyday functioning. Understanding the interplay between early adversity, cognition, and functioning may help guide treatment priorities; cognitive ability is commonly associated with functional competence (McIntyre et al., 2013), and cognitive gains following targeted intervention coincide with improvement in functional ability (Bowie et al., 2013).

Remediation and Plasticity After Childhood Adversity

Despite the well-documented neurocognitive and functional impairment associated with depression, foundational work highlights potential for cognitive plasticity, indicated by the reversibility of these deficits through compensatory strategies and targeted intervention (Bowie et al., 2013). Brain architecture in healthy development shows plasticity throughout adult life, defined as the propensity for adaptive alterations in brain activity and the ability to stimulate neuron-level changes, such as neurogenesis, synaptogenesis, and cortical reorganization, through experience (Greenwood & Parasuraman, 2010). In contrast, other research suggests that early-life experiences influence individual differences in flexible adaptability or lack thereof, and that childhood adversity is related to hindered neurogenesis (McEwen, Gray, & Nasca, 2015; Shonkoff et al., 2012). No previous work has explored whether cognitive functioning among individuals who endured early adversity can be restored through intervention; the current project aims to resolve whether childhood adversity is related to plasticity, evidenced by change in cognition following cognitive remediation – a leading treatment for restoring neurocognition and functional competency.

Cognitive remediation (CR) is defined as "a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition, and meta-cognition) with the goal of durability and generalization" (Cognitive Remediation Experts Workshop, 2010, quoted in Barlati, Deste, De Peri, Ariu, & Vita, 2013). Strategy-based and restorative approaches are elements of CR and are exemplified by the interventions described in the current study. Strategy-based treatment employs "thinking strategies" to assist in completing cognitive tasks, such as combining individual pieces of information in semantically-related groups (i.e. chunking), creating meaning among seemingly non-related items to aid information storage, and repetition (e.g. for learning and storing information in long-term memory). This element makes use of compensatory cortical representation for supplementing cognitive skills in the place of neural networks that may have been injured by illness, prior experiences, or other unknown causes. The restorative element entails promoting neurogenesis through repeated practice of cognitive exercises and maintenance of accurate performance by presenting cognitive activities at the optimal level of challenge (Kurtz, 2016). Cognitive skills such as flexibility, memory, planning, processing speed, and attention are targeted. Furthermore, learning new information processing, storage, and retrieval strategies, and transferring cognitive gains to real world tasks are key components facilitated through CR interventions (Kurtz, 2016).

Cognitive remediation has proven to be effective in improving cognition among individuals with MDD (Bowie, Gupta, & Holshausen, 2013). Similar to a mechanism of other antidepressant treatments and therapies, the neurophysiological underpinnings of CR involve increasing prefrontal activation through cognitive exercise which in turn heightens control over the hyperactive limbic region (Porter, Bowie, Jordan, & Malhi, 2013; Meusel, Hall, Fougere,

McKinnon, & MacQueen, 2013). In previous research, MDD among individuals who experienced childhood maltreatment responded only to select treatments and relapsed sooner after intervention compared to the depression of those who did not experience maltreatment (Harkness, Bagby, & Kennedy, 2012). To date, no prior studies have measured response to CR as a function of early adversity endured.

The Current Study

The overarching goal of the current study is to investigate the role of childhood adversity in neurocognition and functional sequalae among individuals with MDD, as well as the relationship of adversity to neural plasticity, indicated by cognitive gains following remediation. Specifically, we examine baseline cognitive variance accounted for by childhood adversity and characteristics of illness that previously demonstrated associations with cognition, including number of episodes, age at diagnosis, and symptom severity. We hypothesize that cumulative childhood adversity (considering severity and number of adversity types endured), more episodes, earlier age of diagnosis, and more severe symptoms will each be associated with more cognitive impairment in adulthood. Furthermore, our project seeks to clarify whether early adversity among individuals with MDD is associated with reduced plasticity, indicated by less cognitive change following CR. It is hypothesized that higher scores of cumulative adversity will be associated with less change in cognition following treatment. Finally, we aim to clarify whether cognition is uniquely related to functional competency based on the extent of childhood adversity endured. We predict that childhood adversity will be negatively related to functioning and that adversity will moderate the relationship between cognition and functioning. Specifically, we suspect that this relationship will be stronger in magnitude among individuals with higher scores of cumulative adversity.

Chapter 2

Methods

Participants

Forty-two individuals were recruited for the current study having already completed a CR treatment protocol through the Cognition in Psychological Disorders lab at Queen's University. Participants were recruited from the out-patient treatment centres in Kingston, Ontario, for the parent studies, where they had already received diagnosis of MDD as part of their medical care. Inclusion criteria were current or previous diagnosis of unipolar MDD, as well as completion of a 10-week CR intervention and the associated baseline and post-treatment assessments. MDD and comorbid diagnoses were confirmed by medical records. Individuals with a medical diagnosis associated with neurocognitive impairment (e.g. dementia, cerebrovascular accident, traumatic brain injury) or a psychotic spectrum diagnosis were excluded, as well as those with an English reading level below Grade 6 (indicated by performance on the Wide Range Achievement Test-Reading Recognition subtest; Wilkinson, 1993), to comprehension of all standardized testing instructions. According to this exclusion criteria, data of three individuals were removed from the final analyses due to diagnosis of schizoaffective disorder (n = 1) and reading level below Grade 6 (n = 2), resulting in a final sample of 39 individuals. The two studies from which participants of the current study were recruited are described below.

The first study employed the use of traditional Cognitive Remediation (tCR) and the second followed an Action-Based Cognitive Remediation (ABCR) protocol. Both treatments consisted of 2 hour sessions twice weekly lasting for a total of 10 weeks, in group format, ranging from 6-8 members. Each treatment included computerized cognitive training,

facilitation of strategy development and modification, application of strategies to everyday situations (through dialogue or role play), as well as an element of goal-setting with an emphasis on seeking cognitive challenge in one's day-to-day environment. ABCR also included role-plays in simulated everyday tasks. There are no differences in neurocognitive outcomes between these forms of CR (both treatments yield moderate to large improvements); however, ABCR was associated with greater improvement in functioning than tCR ($\eta^2 = .53$), attributable to the practical, hands-on application of the role-play exercises (Bowie, Grossman, Gupta, Holshausen, & Best, 2017). Regarding the 42 individuals who agreed to participate in the current study, 36 completed ABCR and 6 completed tCR.

Measures

Measures Administered in the Parent Studies

Symptom measures.

Participants' depressive symptoms were assessed as part of baseline testing prior to starting CR. The pre-treatment assessments employed the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) and the Beck Depression Inventory (BDI; Beck et al., 1961) across tCR and ABCR studies, respectively, as measures of symptom severity prior to starting treatment. Percent of total items endorsed were computed for each to allow a consistent means of comparison (i.e. the total score was divided by 54 possible points on the MADRS, and 63 possible points on the BDI).

Demographic variables.

All demographic variables, including age at baseline, gender, highest level of education, and occupational status (categories defined by the Hollingshead Index; Hollingshead, 1975) were obtained by self-report at the first assessment session.

Estimated premorbid intelligence.

Estimated premorbid functioning was ascertained using the Wide Range Achievement Test, 3rd Edition, Recognition Reading subtest (WRAT-3; Wilkinson, 1993), a measure that is widely used to appraise level of cognitive functioning preceding the influence of psychiatric illness (Lezak, Howieson, Loring, & Fischer, 2004).

Neurocognition.

The neurocognitive battery used in each previous study included standardized tests that have been well-validated for research and clinical settings. The batteries contained tests that capture performance on neurocognitive domains previously found to be impaired in MDD. Raw data were converted to age- and education-corrected standard scores based on normative data from healthy controls, provided by each test's manual. A neurocognitive composite score was calculated by averaging the standard scores of each domain subsequently described.

Executive functioning.

Executive functions are the higher-level cognitive processes that oversee and integrate more basic perceptual skills. The ability to solve problems, switch between tasks, plan ahead, engage in abstract thinking, and monitor one's actions are encapsulated in executive capacity. For the purpose of the current study, three measures of executive functioning were averaged to form the composite variable as subsequently described.

The ability to efficiently organize and systematically retrieve appropriate lexical items comprises one's verbal fluency. The Letter and Category Fluency tests from the D-KEFS (Delis, Kaplan, & Kramer, 2001) were used to assess phonological and semantic fluency, respectively. These required the participant to verbally produce as many words as possible beginning with a specified letter or belonging to the designated category in a 60-second

interval. The dependent variable is the number of correct words produced in this time frame, averaged across each subtest.

Set-shifting requires participants to flexibly switch attention between two salient features or categories of a stimulus. This was measured using the Trails Making Test B (TMT-B; Partington & Leiter, 1949) where the time that it takes individuals to connect 25 encircled numbers and letters in an alternating order is measured as the dependent variable.

The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) Category Switching Task assesses participants' ability to rapidly generate words by category, alternating between two categories while listing items. Individuals must monitor their responses to ensure they are appropriately meeting task requirements, while remaining cognizant of previous verbalizations to avoid repetition. Total correct responses, including correct category membership and switching order, constitutes the dependent variable.

The average of the fluency tests together with TMT-B and D-KEFS category switching scores were used to form the final executive functioning variable.

Attention and working memory.

Attention and working memory describe the ability to simultaneously attend to and manipulate information in short-term memory. The Letter Number Sequencing Test (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) is an auditory working memory task where individuals hear intermixed numbers and letters of increasing length and must mentally reorder the stimuli before repeating them back to the examiner. This requires both the maintenance and manipulation of items in working memory.

Visuo-spatial working memory refers to the same ability to simultaneously store and manipulate information in short-term memory, but in this case, with visual and spatial

information such as remembering the location of items in relation to one another. The Block-Tapping Task (Berch, Krikorian, & Huha, 1998) requires individuals to remember a pattern indicated by the examiner in sequential and reverse order, increasing in length over time. Again, participants must maintain information and manipulate items in their mind. On each measure, total correct responses translate to a standardized score, with the average of scores from both tasks serving as the final attention and working memory variable.

Verbal learning and memory.

The ability to learn new verbal information over repeated intervals constitutes one's verbal learning capacity. The Hopkins Verbal Learning Test (HVLT; Brandt & Benedict, 2001) is a list-learning task of verbal declarative memory. Individuals listen to a 12-word list over three learning intervals. The dependent variable is the number of words correctly recalled by the respondent over three trials.

Visual learning and memory.

The capacity to learn and remember visual details and relative locations of stimuli comprises visual learning and memory. The Brief Visuo-Spatial Memory Test-Revised (BVMT-R; Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996) requires examinees to reproduce a set of visual images in a specified location after a 10-second exposure, and then reproduce the images after two additional exposures. The accuracy of design and location of reproduced visual images and the degree to which learning improves with repeated exposure are rated according to manualized scoring procedures and form the dependent variable.

Processing speed.

Processing speed involves the ability to quickly and accurately respond to stimuli in the environment. This was assessed using the Digit-Symbol Coding Task (Wechsler, 2008) and the

Trail Making Test Part A (TMT-A; Partington & Leiter, 1949). The first of these requires individuals to rapidly and accurately match numbers to random symbols, with the total number of correct responses after 90-seconds as the dependent variable. The second requires the participant to connect 25 consecutive numbers arranged in non-sequential locations on a sheet of paper as quickly as possible, with total time to completion as the variable of interest. Processing speed in the current study is indicated by the average of the two standardized scores resulting from these tasks.

Composite score of cognition.

The same tests were administered at baseline and immediately following treatment, with different versions of select tests being used to counteract practice effects. The final composite score was derived by taking the average of *t*-scores across cognitive domains, equally-weighted, resulting in a composite neurocognitive variable for both times of measurement.

Functional competence.

The ABCR study used the finance and communication subscales of the Brief University of California San Diego Performance-Based Skills Assessment (UPSA-B; Mausbach et al., 2007), which require the participant to perform fictitious financial tasks (scored on a scale of 0 to 6) and demonstrate communication skills in different settings (scored on a scale of 0 to 9), respectively. The tCR study did not employ this measure, and accordingly, the analysis examining functional competence is based on a subset of the total sample (n = 33).

Measures Administered in the Current Study

Illness characteristics.

Current MDD status was assessed as part of participation in the present study using the Mini-International Neuropsychiatric Interview (M.I.N.I.) module for MDD to examine whether current illness status was related to responses on the semi-structured interview on childhood adversity. The measure of symptom severity administered at the time of baseline cognitive testing, upon initial enrollment in the parent studies, is used for all other analyses. Comorbid diagnoses and age at diagnosis were obtained via medical file upon initial enrollment. Number of episodes prior to starting CR were provided by self-report and then transformed into an ordinal variable representing 1, 2, 3, 4, 5, 6, or 7≤ episodes. Our decision to represent number of episodes in this manner followed the example of previous studies that employed an ordinal scale to capture retrospectively reported episode frequency (e.g. Kessing & Andersen, 2004; Vanderhasselt & Raedt, 2009). We chose 7 as the end point given the relatively consistent distribution of individuals in our sample who reported 1 through 6 episodes, and also considering the wide range of episode frequencies above this point that were observed to be less precise estimations (i.e. participants who endured a high frequency of episodes tended to report more ball-park estimates). Furthermore, we presume that consequences associated with the stress of repeated episodes may demonstrate less variability beyond a certain point, and based on our data, 7 was a logical cut-off.

Childhood adversity.

The Childhood Experience of Care and Abuse interview (CECA; Bifulco, Brown, & Harris, 1994) is a semi-structured contextual interview that retrospectively assesses adversity occurring across 6 domains: (1) parental antipathy, measuring harsh, critical parenting (ratings

assigned for each primary caregiver); (2) parental indifference, including neglect of the child's physical and/or emotional needs (assigned for each primary caregiver); (3) discord and violence between parents; (4) physical abuse directed towards the child by parents; (5) sexual abuse, involving non-consensual sexual encounters with any offender; and (6) bullying directed at the individual from same-age peers. The interview obtains information about experiences of abuse from as far back as the participant can remember up until age 17. Information about the frequency, duration, and timing of exposure is obtained, as well as the provision of concrete examples. Interviewers are trained not to query about depression status or subjective interpretation of events. Rather, concrete examples are rated on a 4-point severity scale (1 = marked, 2 = moderate, 3 = some, 4 = little/none) and compared to the criteria specified in the CECA manual, which includes a multitude of examples and rating rules. A second rater independently rated 25% of CECA vignettes and the kappa coefficient was .89.

Ratings across all domains were summed to comprise the cumulative adversity variable and then reverse-coded for ease of interpretation, such that higher scores are indicative of more severe and multiple types of adversity. In addition, domain-specific variables of adversity were achieved by dichotomizing the ratings on each scale into severe (ratings of *marked* or *moderate*) versus non-severe (ratings of *some* or *little/none*). This dichotomization is consistent with common practice in the literature for examining domain-specific adversity (e.g. Bifulco et al., 1994; Harkness, Bruce, & Lumley, 2006), and yields a less skewed distribution of data. As ratings of antipathy and neglect are assigned for two primary caregivers as part of the CECA, a conglomerate variable representing emotional maltreatment was created, where a rating of *severe* in antipathy or neglect for either caregiver would merit a rating of severe emotional maltreatment.

Procedure

Individuals from the original studies were recruited by telephone to participate in the current project. Those who agreed to participate came into the lab for one session lasting approximately 1.5 hours and were compensated $40 for their time. The current assessment occurred approximately 2-3 years following participants' initial cognitive assessment and enrollment in the CR intervention. All assessments were conducted by the primary investigator, a graduate student in a clinical psychology program. The session began with participants providing their written informed consent upon reviewing the letter of information. The M.I.N.I. module for MDD was administered to identify current illness status, and estimated number of episodes before initial participation was obtained by self-report. Next, the CECA interview was administered, followed by a debrief of experimental procedures and provision of community mental health resources. Ethics approval was granted for this study by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB; see Appendix A for letter of ethics clearance).

Data Analysis

A multiple regression model was used to assess how childhood adversity and characteristics of illness explain variance in baseline cognition. First, Pearson correlations were conducted to identify the dependent variables that were univariately correlated with baseline cognition in our sample. Cumulative adversity, number of episodes, and age at diagnosis demonstrated significant associations and continued to the next phase of the analysis. Estimated premorbid IQ was entered as a controlled variable to account for level of cognition independent of the effects of illness. Then, cumulative childhood adversity, number of episodes, and age at diagnosis were entered.

Follow-up hierarchical multiple regressions were conducted to assesses the relationship between cumulative adversity and specific cognitive domains. This included five analyses to examine the respective associations of the independent variable with executive functioning, attention and working memory, verbal learning and memory, visual learning and memory, and processing speed. Premorbid IQ was entered as a covariate in each analysis. The Bonferroni post-hoc correction was applied to account for multiple analyses (.05/5), yielding $p < .01$ as the criterion for significance.

An additional follow-up multiple regression was conducted to identify types of adversity associated with cognitive impairment. Emotional maltreatment, physical maltreatment, sexual maltreatment, parental discord, and bullying were entered as predictor variables after controlling for premorbid IQ, with baseline cognition as the outcome.

To examine the association between childhood adversity and response to CR, we regressed cumulative adversity on post-treatment cognitive scores, controlling for pre-treatment cognition in the first block.

Finally, we used a hierarchical multiple regression model to identify if there was a significant interaction between cognition and severe adversity. Then, simple effects were probed using Hayes' (2017) PROCESS 3.3 macro for moderated regression.

Chapter 3

Results

Descriptive Statistics

Participants

Participant demographic statistics are summarized in Table 1. Age of first psychiatric hospitalization ranged from 5 to 59 years (M = 28.29, SD = 14.72), although approximately 51% of participants were never hospitalized. Among those who were, the number of times hospitalized ranged from 1 to 30 (M = 4.8, SD = 7.37). Across assessment points, all participants were community-dwelling. Approximately 8% had a history of alcohol dependence, 36% had at least one comorbid anxiety disorder, and 5% had a comorbid personality disorder. Twenty-seven participants (69%) were taking psychotropic medication at the time of initial cognitive testing and enrollment in CR (see Table 2 for a distribution of medication use).

Table 1.

Participant demographics (N = 39).

Age M (SD)	46.87 (12.76)
Sex *n* (%)	
Male	12 (30.8%)
Female	27 (69.2%)
Ethnicity *n* (%)	
Caucasian	34 (87.2%)
Asian	2 (5.1%)
Hispanic	2 (5.1%)
Arabic	1 (2.6%)
Highest Education Achieved *n* (%)	
Some high school	-
High school diploma/GED	1 (2.6%)
Some college/university	8 (20.5%)
College or university degree	13 (33.3%)
Post-graduate degree	4 (10.3%)
Undeclared	13 (33.3%)
Total Years of Education M (SD)	15.59 (1.55)
Occupational Status	
Employed	9 (23.1%)
Unemployed	25 (64.1%)
Student / homemaker / retired	3 (7.7%)

Table 2.

Frequencies of participant medication use.

	N	*%*
Selective Serotonin Reuptake Inhibitors	13	33.33
Serotonin-Norepinephrine Reuptake Inhibitors	9	23.08
Benzodiazepines	6	15.38
Non-barbituate sedatives	4	10.26
Tricyclics	4	10.26
Tetracyclics	4	10.26
Lithium	2	5.13
MAO Inhibitors	1	2.56
Other	7	17.95
No medication reported	12	30.77

tCR vs. ABCR Descriptive Statistics

No significant difference was observed across samples from each parent study in cumulative childhood adversity, $t(37) = -.09$, $p = .93$, age of diagnosis, $t(37) = .45$, $p = .66$, number of episodes, $t(37) = -.88$, $p = .39$, symptom severity, $t(37) = -1.57$, $p = .12$, or baseline cognition, $t(37) = 1.23$, $p = .23$. Table 3 shows descriptive statistics for all independent and dependent variables. In addition, no significant differences were observed in age at baseline, $t(37) = .59$, $p = .56$, sex, $\chi^2(1) = .02$, $p = .88$, highest education, $\chi^2(4) = 8.72$, $p = .07$, total years of education, $t(24) = .57$, $p = .57$, or occupational status, $\chi^2(7) = 3.88$, $p = .79$. There was a significant difference observed across samples in ethnicity, $\chi^2(3) = 14.14$, $p = .003$.

Table 3.

Means and standard deviations for independent and dependent variables.

	tCR Sample (*n* = 6)		**ABCR Sample (*n* = 33)**		**Total Sample (*N* = 39)**			
	Mean	SD	Mean	SD	Observed Range		Mean	SD
Premorbid IQ *(WRAT t-score)*	-	-	54.18	5.78	38	62	54.05	5.31
Childhood Adversity *(score of 0 to 32)*	8.17	5.84	7.97	5.01	0	19	8.00	5.06
Age at Diagnosis	31.67	15.29	34.85	16.02	10	66	34.36	15.76
Number of Episodes *(from 1 to 7≤)*	6.33	1.21	5.64	1.87	1	7≤	5.74	1.79
Symptom Severity *(percent of total symptom items endorsed)*	.54	.13	.42	.19	.10	.94	.43	.19
Baseline Cognition *(t-score)*	43.62	3.58	48.01	8.52	19.29	66.43	47.34	8.08
Post-Treatment Cognition *(t-score)*	49.55	3.68	51.63	6.62	38.27	66.84	51.31	6.26
Baseline Functioning *(UPSA total score from 0 to 26)*	-	-	88.8	10.76	62.5	100	88.8	10.76

Current MDD Status

A further comparison was made within our sample regarding the difference in reported adversity as a function of current depression status. Approximately 59% of individuals were in an active episode at the time of the CECA interview. Results indicated no difference in reported adversity based on whether or not an individual was in an episode of depression at the time of the interview, $t(37) = .70$, $p = .49$. A summary of adversity types endorsed by the overall sample is provided in Table 4.

Table 4.
Frequency of participants experiencing severe adversity by category.

N = 39	*n (%)*
Emotional Maltreatment	22 (56.4)
Physical Maltreatment	14 (35.9)
Sexual Maltreatment	12 (30.8)
Parental Discord	10 (25.6)
Bullying	14 (35.9)

Childhood Adversity, Characteristics of Illness, and Cognition

The relevant assumptions required for multiple regression were tested and confirmed that no independent variables were correlated as indicated by tolerance and variance inflation factors well within accepted limits (greater than .2 and lower than 10, respectively). Residual and scatter plots indicated the assumptions of normality, linearity, and homoscedasticity were all satisfied. As 6 participants did not complete the measure of premorbid functioning, data were sorted according to education and the average of the nearest 8 premorbid IQ scores was used to impute missing values.

Pearson correlations were conducted to identify characteristics of illness that were significantly associated with baseline cognition, revealing that age at diagnosis and number of episodes were significantly correlated with cognition, $r = .33$, $p = .04$, and $r = -.44$, $p = .006$, but symptom severity was not, $r = -.24$, $p = .145$. Thus, only age at diagnosis and number of episodes proceeded to the next phase of the analysis. To test the hypothesis that childhood adversity and characteristics of illness explain variance in cognition, a hierarchical multiple regression was conducted with baseline cognition as the dependent variable. Premorbid IQ was entered as a controlled variable, intended to account for differences in cognitive function prior to the influence of psychiatric illness. This measure also served to hold differences in cognition that may be attributable to education level or SES constant. Then, cumulative adversity, age at diagnosis, and number of episodes were simultaneously entered in the model.

Consistent with our hypothesis, a significant regression equation was found for explaining variance in baseline cognition in step 2 after controlling for premorbid IQ, $F(1, 36) = 7.31$, $p < .001$, $\Delta R^2 = .374$. Cumulative adversity and number of depressive episodes were significant predictors of baseline cognition, $\beta = -.45$, $t(36) = -3.34$, $p = .002$, and $\beta = -.33$, $t(36) = -2.53$, $p = .017$. The association between childhood adversity and baseline cognition is visualized in Figure 1. Intercorrelations between regression variables are reported in Table 5 and regression statistics are reported in Table 6.

Post-hoc power analysis was conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) and indicated that with a sample of 39 individuals, the given effect size of $f^2 = .60$, and $\alpha = .05$, achieved power is .97.

Figure 1. The association between childhood adversity and baseline cognition.

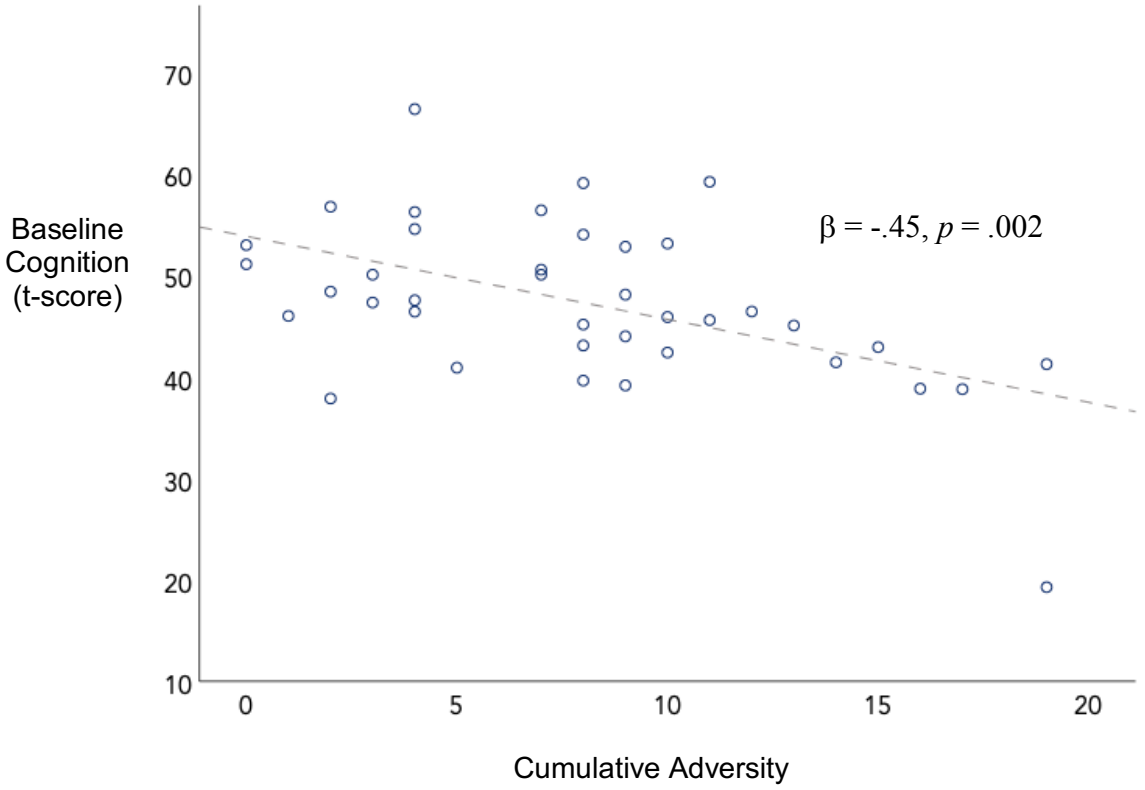


Table 5.

Intercorrelations among regression model variables.

	1	2	3	4	5
1. Cognition	-				
2. Premorbid IQ	.30*	-			
3. Childhood Adversity	-.51**	-.33*	-		
4. Age at Diagnosis	.33*	.22	-.05	-	
5. Number of Episodes	-.44**	-.25	.15	-.14	-

*$p < .05$
**$p < .01$

Table 6.

Hierarchical regression output for childhood adversity and characteristics of illness associated with baseline cognition.

	Unstandardized Coefficients								
	b	*SE*	β	*t*	*p*	R^2	ΔR^2	ΔF	*p*
Model 1						.088	.088	3.59	.066
Premorbid IQ	.45	.24	.30	1.90	.066				
Model 2						.462	.374	7.88	.000
Premorbid IQ	.02	.21	.01	.09	.932				
Childhood Adversity	-.71	.21	-.45	-3.34	.002				
Age at Diagnosis	.13	.07	.26	2.02	.051				
Number of Episodes	-1.48	.59	-.33	-2.51	.017				

N = 39. Premorbid IQ as indicated by WRAT *t*-scores. Childhood adversity indicated by cumulative trauma score on the CECA semi-structured interview. Age of diagnosis obtained by medical file. Number of episodes as an ordinal value obtained by self-report.

Domain-Specific Impairment Associated with Childhood Adversity

Follow-up analyses were conducted to identify domains of cognition particularly associated with childhood adversity. Five hierarchical multiple regressions were employed, again controlling for Premorbid IQ in the first step, then assessing the relative association of cumulative adversity with executive functioning, attention/working memory, verbal learning/memory, visual learning/memory, and processing speed. Descriptive statistics for scores across cognitive domains are enclosed in Table 7.

Table 7.

Descriptive statistics of cognitive domain *t*-scores.

	Observed Range		M	SD	Skewness	
					Statistic	SE
Executive Functioning (Average of DKEFS Fluency, Category Switching, and TMT B)	19.1	75.2	49.44	10.23	-.33	.38
Attention/Working Memory (Average of Letter Number Sequencing & Spatial Span)	25	69	47.99	9.81	.04	.38
Verbal Learning/Memory (HVLT)	31	73	48.28	10.38	.28	.38
Visual Learning/Memory (BVMT)	25	69	47.29	10.26	-.18	.38
Processing Speed (Average of TMT A & Digit Symbol Coding)	-3.65	62.95	45.67	11.91	-1.96	.38

After our significance criterion was corrected using the Bonferroni post-hoc method (.05/5 = .01), a significant association was detected for visual learning/memory, $\Delta R^2 = .214$, $\Delta F(1, 36) = 10.21$, $p = .003$. The association between cumulative adversity and processing speed was approaching significance, $\Delta R^2 = .154$, $\Delta F(1, 36) = 6.61$, $p = .014$. Table 8 includes results of all domain analyses. Figure 2 depicts a linear relationship between childhood adversity and visual learning/memory.

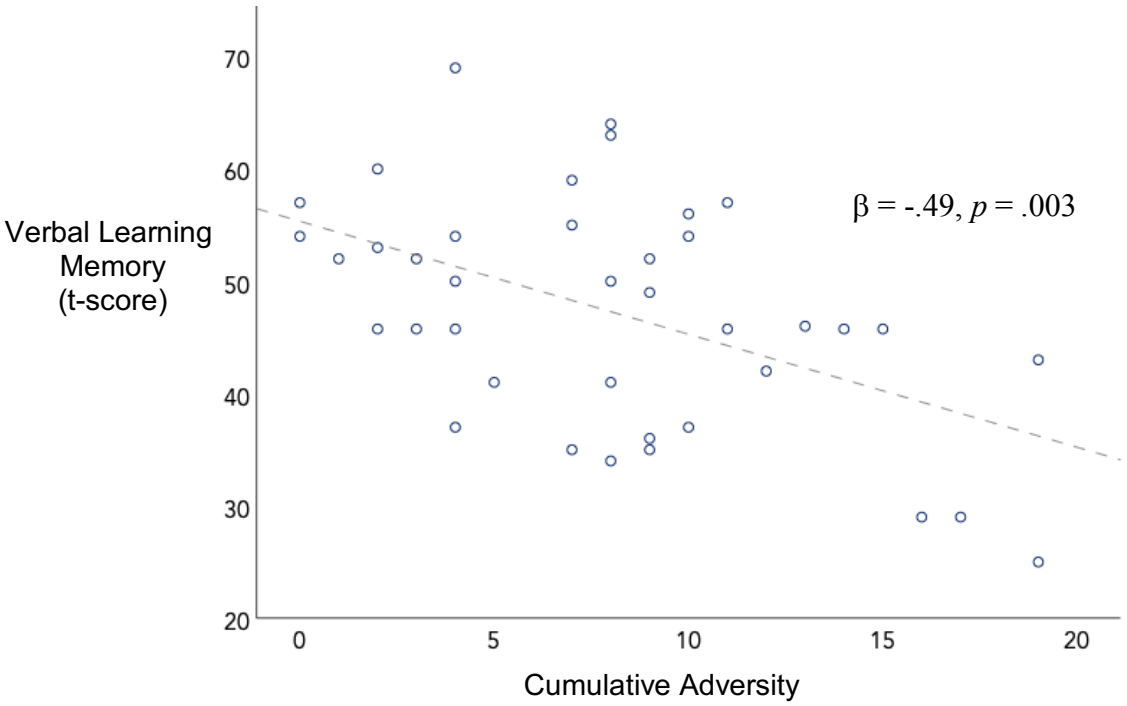
Table 8.

Regression coefficients of childhood adversity and cognitive domain *t*-scores.

	β	*t*	*p*
Executive Functioning	-.27	-1.76	.088
Attention/Working Memory	-.28	-1.75	.089
Verbal Learning/Memory	-.32	-1.92	.062
Visual Learning/Memory	-.49*	-3.20	.003
Processing Speed	-.42	-2.57	.014

*significant after post-hoc correction

Figure 2. The association between childhood adversity and visual learning/memory.



Types of Adversity Associated with Cognitive Impairment

A follow-up multiple regression analysis was conducted to identify the relative contributions to cognitive variance explained by types of adversity. Dichotomized adversity domains were entered simultaneously into the model, after controlling for premorbid IQ. Examination of variable coefficients, depicted in Table 9, revealed that parental discord was the only type of adversity that independently contributed to cognitive variance, β = -.41, $t(32)$ = -2.38, p = .023.

Table 9.

Regression coefficients of adversity types and cognition.

	β	*t*	*p*
Emotional Maltreatment	-.12	-.68	.501
Physical Maltreatment	.13	.67	.507
Sexual Maltreatment	-.26	-1.61	.117
Parental Discord	-.41*	-2.38	.023
Bullying	-.25	-1.71	.096

*significant at $p < .05$

Childhood Adversity and Response to Cognitive Remediation

A paired-samples *t*-test was conducted to compare baseline cognition ($M = 47.34$, $SD = 8.08$) to post-treatment cognition ($M = 51.31$, $SD = 6.26$). Results indicated a significant improvement following treatment, $t(38) = -4.58$, $p < .001$, Cohen's $d = .73$.

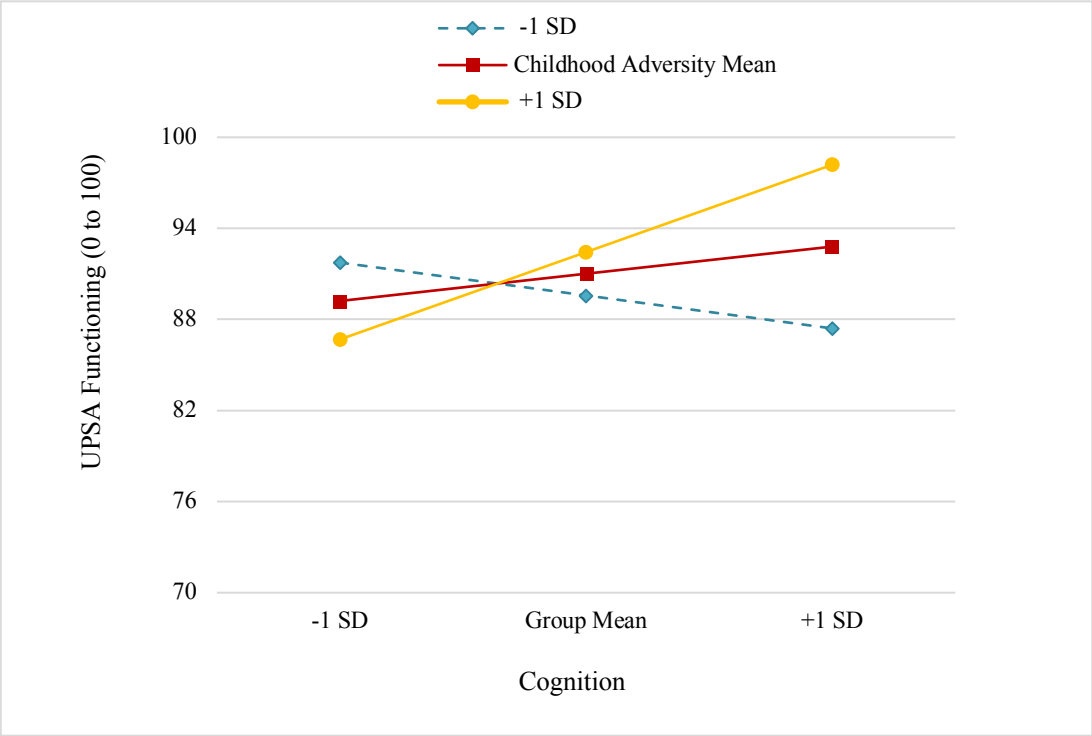
To test the hypothesis that childhood adversity is associated with less plasticity following treatment, indicated by less cognitive change following CR, a two stage regression model was conducted with baseline cognition and cumulative adversity as independent variables and post-treatment cognition as the dependent variable. After controlling for baseline cognition, childhood adversity accounted for a small amount of variance in the opposite direction than hypothesized; greater extent of adversity was correlated with more improvement following treatment, $\beta = .26$, $t(36) = 2.09$, $\Delta R^2 = .05$, $\Delta F(2, 36) = 4.36$, $p = .044$.

Childhood Adversity as a Moderator of Cognition and Functioning

Overall impairment observed on the UPSA-B was comparable to scores from a previous study that found the UPSA-B to be sensitive to functional performance in MDD (M = 88.8, SD = 9.88; Milanovic, Holshausen, Milev, & Bowie, 2018).

To test the hypothesis that severe childhood adversity moderates the relationship between cognition and functioning, a moderated regression was conducted. First, we used a hierarchical regression model to identify if there was a significant interaction effect. In the first step of the model, the two predictor variables were included: baseline cognition and cumulative childhood adversity. These variables together did not account for variance in function, R^2 = .104, F (2, 30) = 1.74, p = .193, although adversity was independently associated with functional ability, b = -4.10, t(37) = -2.51, p = .018. An interaction term for baseline cognition and childhood adversity was created and added to the regression model, and significantly accounted for variance in functioning, ΔR^2 = .177, ΔF(1, 29) = 7.16, p = .012. The PROCESS 3.3 macro was used to probe conditional effects (Hayes, 2017). Examination of the interaction, depicted in Figure 3, shows that cognition was positively related to functioning only for individuals who experienced high levels of adversity (defined as 1 standard deviation above the group mean; b = .63, SE = .25, p = .018, 95% CI = .11, 1.15). Regression coefficients of the final model are included in Table 10 and conditional effects are reported in Table 11. The normal *P-P* plot confirmed that residuals were normally distributed, and *Levene*'s test verified the equality of error variances, F(1, 31) = 1.41, p = .25. Post-hoc power analyses of ΔR^2 of the interaction term, with 33 participants and the given effect size (f^2 = .22), yields power of .73.

Figure 3. Cognition and functioning based on childhood adversity.



Cognition and functioning are positively associated only for individuals who experienced high levels of childhood adversity (1 SD above group mean).

Table 10.
Regression coefficients of cognition and childhood adversity on functioning.

	b	*SE*	*t*	*p*	95% CI for *b*	
Cognition	-.57	.45	-1.27	.21	-1.49,	.35
Childhood Adversity	-4.10	1.63	-2.51	.018	-7.43,	-.76
Cognition x Adversity	.09	.03	2.67	.012	.02,	.16

Table 11.
Conditional effects of adversity.

	b	*SE*	*t*	*P*	95% CI for *b*	
- 1 SD below mean	-.30	.37	-.81	.427	-1.05,	.46
Group mean	.17	.26	-.63	.530	-.37,	.71
+1 SD above mean	.63	.25	2.50	.018	.11,	1.15

Chapter 4

Discussion

This study examined how childhood adversity and characteristics of illness explain variance in neurocognition among individuals with MDD, and found that both early adversity and number of depressive episodes were significantly associated with cognitive impairment. In addition, individuals who experienced early adversity demonstrated cognitive plasticity, indicated by change in cognitive scores following targeted treatment. Finally, our findings indicated a relationship between cognition and functioning only for individuals with high scores of cumulative adversity.

The Relationship Between Cumulative Childhood Adversity and Baseline Cognition

Consistent with our hypothesis, results showed that childhood adversity was negatively associated with cognitive performance in adulthood among individuals with MDD, even after controlling for premorbid IQ. We examined cumulative severity across different forms of adversity endured by individuals from birth to age 17, which encapsulate critical years of brain development and a period when neurophysiology is particularly sensitive to threat. Former studies highlighted relationships between types of abuse and specific cognitive facilities but were limited by only including healthy participants or not examining the cognitive profile of depressed individuals who did not experience adversity. In addition, preceding studies did not account for normal variation in premorbid cognition in their models. Nonetheless, current results converge with previous findings and also highlight a dose-sensitive relationship between the pervasiveness and severity of adversity and global cognitive deficits. Furthermore, this project employed a more reliable measure of childhood adversity and used a sample of individuals with MDD who endured a range of adverse experiences.

While it is difficult to ethically examine the causal relationship between childhood trauma and subsequent cognitive dysfunction in humans, animal models provide some evidence for how these variables relate to one another in causality. In rodent studies, impaired memory and compromised long-term potentiation (a mechanism critical for the encoding of memory) directly resulted from a manipulated stress condition (Ivy et al., 2010). Furthermore, studies with primates have demonstrated that repeated separations from the mother, inconsistent maternal feedings, and maternal abusive behaviour are associated with many neurological changes that contribute to alterations of the HPA axis that persist for years after the initial stressor subsided (Sánchez et al., 2005; Coplan et al., 1996; Sánchez, 2006). Experiments of nature demonstrate similar neurological consequences, as in the case of the Bucharest Early Intervention Project. In this controlled trial, Romanian orphans were randomly assigned to high-level foster care or continued institutional care. The profound consequences of neglect on neurological functioning were highlighted, as well as the potential for reversing such negative outcomes upon placement in a more nurturing environment (Smyke, Zeanah, Fox, & Nelson, 2009; Chugani et al., 2001; Carlson & Earls, 1997). It is suspected that similar mechanisms are driving the results observed in the present analysis.

Nonetheless, the possibility of a reversed causal direction between these variables must not be negated; cognitive impairment in childhood may drive dysfunction in the home and maltreatment from primary caregivers or other perpetrators. A child who demonstrates impaired cognition and associated limitations in their communication and psychosocial skills could be a stressor for care providers, potentially perpetuating discord and eliciting antipathy or neglectful behaviour. Furthermore, impaired cognition or psychosocial awareness of a child may lend to an easier execution of wrongful actions from adult perpetrators or same-age peers.

Previous work that identified impaired memory following a manipulated stress condition aligns with our findings that adversity was most strongly associated with memory and learning deficits of all the cognitive domains. Our cumulative adversity variable is likely indicative of early stress endured, and our results demonstrate a clear linear relationship between the extent of stress and the degree of cognitive impairment. Additionally, our subsequent analysis, as later described, suggests that deficits in cognition among individuals who experienced early trauma can be reversed in the appropriate context of cognitive intervention.

Number of depressive episodes was the only characteristic of illness that significantly contributed to our model; unsurprisingly, more episodes were associated with poorer baseline cognition. Gorwood et al. (2008) found a similar association between increased number of episodes and enduring memory impairment. These authors speculated that the repeated stress of illness exerts a toxic effect on cognition. In contrast, results from another study suggested that lower cognitive reserve precedes persistent episodes (Koenen et al., 2009). At the same time, a different line of evidence highlights hippocampal volume as a potential confound and pre-existing risk factor for recurring episodes and cognitive impairment following traumatic events (Lupien et al., 2009; Gilbertson et al., 2002).

We postulate that other characteristics of illness may largely relate to cognition through their shared association with childhood adversity, which would explain why we did not find a significant relationship between cognition and symptom severity. Cognitive deficits appear to be more stable than the cyclical nature of depressive symptoms and persist even in states of remission. One study revealed that up to 57% of individuals who experienced cognitive impairments while depressed continued to experience deficits after symptoms resided

(Reppermund, Ising, & Zihl, 2009). Other work suggested only a small association between symptoms and cognitive performance (McDermott & Ebmeier, 2009). Although more distal to the setting of cognitive assessment, the influence of early experiences on the long-term expression of illness and cognitive function appears to be much stronger.

As we did not find a significant association between cognition and age at diagnosis, we highlight potential noise due to the variability in time before true illness is formally identified. Obtaining a valid retrospective account of age at illness onset poses a challenge for psychopathology research in general, and is also a limitation of the present study measures. Still, it is possible that accounting for variance explained by childhood adversity and number of episodes may have precluded independent variance explained by age at diagnosis. Another point of consideration is that cognitive impairment experienced by later-onset patients may be different from that of individuals whose depression came earlier in life. Herrmann et al. (2007) found that patients with early onset MDD suffered predominantly from impaired episodic memory, and those with late onset from deficits in executive functioning and processing speed. Our analysis did not capture the unique associations between age at diagnosis and specific cognitive domains, and such nuances may have been lost in looking only at a composite measure of ability.

Domain-Specific Impairment

After post-hoc corrections for multiple analyses, visual learning/memory was individually associated with cumulative childhood adversity, and a trend was observed for processing speed and verbal learning/memory. Stress-mediated neurological effects include hindered neurogenesis, inappropriate pruning of synapses, and inadequate myelination, which are particularly pertinent for stress-susceptible brain regions such as the hippocampus,

amygdala, prefrontal cortex, and white matter tracts (Teicher & Samson, 2016). The compromised anatomy of the hippocampus, which primarily houses skills required for learning and memory, may partly explain why these facilities are implicated among affected individuals. Similarly, stress-sensitivity of white matter tracts may illuminate why individuals with a history of childhood adversity exhibit poorer processing speed. Benedetti et al. (2014) found an inverse relationship between number of adverse childhood experiences and axial diffusivity of white matter tracts, a measure conveying the integrity and coherence of neural communication networks. In another vein of research, Turken et al. (2008) found that processing speed was related to the structural integrity of white matter tracts.

Our investigation did not identify a significant association between childhood adversity and executive function, which contradicts previous literature as well as the notion that cognitive domains particularly affected should align with stress-sensitive brain regions like the prefrontal cortex. One explanation for why we did not find a significant relationship between these variables involves the time period of adversity that was assessed. Past findings convey a greater impact of stress experienced during adolescence to early-adulthood on the prefrontal cortex (Andersen & Teicher, 2009; Sinclair, Webster, Wong, & Weickert, 2011). Our measure did not assess adversity experienced from age 18 onwards, neglecting a portion of the prefrontal developmental period. Emerging evidence indicates that timing of stress exposure is a crucial determinant of cognitive deficits that result, with brain regions being most sensitive when undergoing development or major changes (Lupien et al., 2009). Another possibility is that our measure of executive functioning did not comprehensively assess the range of skills that comprise executive functions such as inhibitory control, organization, planning, and task initiation, to name a few. Finally, the sample size of the current study may have limited

statistical power to detect true effects, which is a plausible explanation given the similar effect sizes relative to other domains.

Types of Adversity Associated with Cognitive Impairment

A follow-up analysis to identify the particular types of childhood adversity associated with cognitive deficits revealed a significant relationship only with parental discord. Again, limitations in power require that results be interpreted with caution. Taken at face value, a holistic measure of adversity demonstrated a clear, graded relationship with deficits in cognition that was not observed in the case of most of the dichotomized variables representing individual types of maltreatment. It is possible that the dichotomization of these variables may have limited our ability to detect the dose-sensitive nature of their relationship to cognition. Also, parental discord may be unique from other forms of adversity as it tends to represent a more stable experience of tension and hostility, as opposed to other forms that could occur in contained instances (e.g. distinct incidents of sexual abuse, bullying limited to the school environment, a severe episode of physical punishment, etc.). In previous animal and human studies, it is chronic early-life stress, as opposed to acute occurrences, that has been found to influence life-long cognitive and affective processes (Chen & Baram, 2016). With this rationale, we would also expect that an overarching dynamic of antipathy with primary caregivers would be significantly related to chronic stress and cognitive impairment. This logic has been supported in previous work, where abnormal patterns of maternal care, including neglect, inconsistency, and lack of sensitivity, were associated with long term consequences for cognitive and affective processing (Chen & Baram, 2016). Furthermore, many previous studies focused on the quality or absence of maternal care; in contrast, there is a gap in the literature

surrounding the influence of paternal nurturing or abusive behaviour. Examining the respective contribution of maternal and paternal caregiving dynamics may provide additional insight.

Additionally, it is worth noting that previous work identified dimensions of maltreatment related to performance on specific cognitive tasks (Gould et al., 2013). Consequently, the examination of disparate forms of adversity with a composite measure of cognition in the current study may not have captured the nuanced reality of these relationships. However, we presume that parsing out the influence of separate forms of adversity on distinct cognitive skills would show similar relationships to those observed by Gould et al. (2013). Similarly, delineating the differences associated with having at least one positive and caring caregiver may also influence outcomes associated with maltreatment in any one domain; previous evidence highlights the resilience-enhancing effect of a positive relationship with a competent adult in the face of other forms of adversity (Masten, Best, & Garmezy, 1990).

Plasticity After Childhood Adversity

Our analysis revealed a significant but small association between childhood adversity and response to CR but in the opposite direction than hypothesized; higher scores of cumulative adversity were related to more improvement following treatment. Although this association could be partly a result of lower baseline scores having more room for improvement in the first place, lessons from gene expression provide an alternative rationale for the indication of neuroplasticity following treatment among maltreated individuals. McEwen et al. (2015) examined the genetic profile of the hippocampus in stress-exposed mice and found that after a recovery period, anxiety-like behaviours returned to pre-stress baselines even though the expression of genes remained distinct from stress-naïve controls. These authors extrapolated that desired behaviours could be restored but through the representation of

alternate neural networks. Parallel pathways inherent in our neural architecture allow multiple means of cortical representation so that our cognition and behaviour are not only dependent on the integrity of any one particular network. This means that irrevocable changes to certain circuitry can be compensated for by changes to other pathways in our brain. A relevant example from animal studies regards the compensatory nature of an enriched environment (consisting of larger peer groups, stimulating toys, and a complex cage layout) following maternal neglect that demonstrated a reversal of learning and memory deficits indicated by performance during a maze task that required hippocampal-dependent learning (Ganzel & Morris, 2011). Another animal study identified that environment enrichment during adolescence attenuated many of the neural and behavioural consequences of maternal separation (Lu et al., 2003). In humans, interventions such as CR that foster compensatory mechanisms and provide opportunity for cognitive challenge could align with an ideal approach to recompense for cortical regions that may have suffered from the toxic effects of childhood trauma.

Cumulative Adversity as a Moderator of Cognition and Functioning

Our sample was characterized by relatively in-tact functional performance on finance and communication tasks; however, a noteworthy difference in the relationship between cognition and functioning emerged as a function of adversity. While cognition among individuals with high scores of childhood adversity was significantly associated with functional performance, we did not identify an association between cognition and functioning among those who experienced average or below average levels of adversity. In addition, there was a significant main effect of adversity, but cognition was not related to functioning in the overall sample. As speculated in our rationale, the particular weaknesses associated with adversity may

be especially pertinent for tasks of everyday functioning. Another interpretation may be that individuals who experienced childhood trauma are especially dependent on their cognitive reserve to effectively carry out functional tasks.

It is less clear why we did not identify a significant association between cognition and functioning as a whole, although restricted sample size and factors unique to our sample must be considered as plausible rationale. It would be helpful to investigate other characteristics of individuals who comprised this group in order to understand why we did not observe a relationship that has been well validated across many previous studies. Future work is needed to replicate our findings and elucidate specific mechanisms through which these common targets of treatment are related.

Limitations and Future Directions

The characteristic theme of our study limitations surrounds factors inevitably contributing to variance in our modeled relationships that were not accounted for due to restrictions in sample size and methodology. This includes variables related to the quality of adversity, such as timing and duration of exposure, sex differences in response to stress, as well as the more nuanced relationships between the types of maltreatment and particular cognitive domains. Furthermore, the impact of additional stress encountered in adulthood on cognition and functioning, in addition to that which is experienced in early years, is important to inform a comprehensive understanding of the sequalae of stress across the lifespan. Finally, our methods were not able to account for the role of protective variables that may serve to attenuate the negative association of early trauma with future outcomes.

The few previous studies on childhood trauma as related to neurocognition in adulthood examined only the particular domains of abuse as associated with precise areas of cognition.

While our study accounts for the global impact of childhood trauma on overall cognitive performance, there is an additional story to be told regarding the nature of specific events that happen during development and precise consequences associated with each. Before we can conclude that global cognitive functioning is implicated among affected individuals, future work is required to replicate and clarify the relation of specific cognitive facilities with cumulative adversity endured. Neuroimaging studies have also employed a domain-specific approach, and across this research an interesting theory emerges regarding the adaptive way in which the brain responds to trauma. Namely, specific types of abuse appear to target brain regions and pathways that process and convey the associated aversive experience. In the case of verbal abuse, witnessing domestic violence, and sexual abuse, brain areas responsible for auditory, visual, and somatosensory processing are impacted, and domains of verbal and visual cognitive functioning show associated deficits (Teicher & Samson, 2016; Gould et al., 2013). Similarly, emotional abuse shows associations with enhanced amygdala response to emotional faces and diminished striatal response to anticipated rewards, as well as emotional processing deficits (Teicher & Samson, 2016; Gould et al., 2013). Further work should clarify and validate the relationships between abuse domain and neurocognitive functions, as well as how adversity relates to other impairing characteristics of depression such as reduced motivation and impaired reward-sensitivity.

In addition, it is unclear whether there is a critical threshold of trauma exposure associated with deficits in adult functioning, or particular ages that render an individual differentially susceptible to the impact of trauma. As noted, there is empirical support that stress particularly influences brain structures whose development coincides with the timing of trauma. It is less clear how the duration of exposure associates with cognition and other

outcomes, although intuitively, longer exposure may preclude the opportunity for the "enriched environment" effect, or the ability of resilience-enhancing mechanisms to promote restoration of normative functioning. Future work with a large and diverse enough sample may be able to disentangle the outcomes associated with these experiential nuances.

Another distinction not addressed are the personal characteristics that may influence response to adversity, with an important individual factor being gender. Female hippocampi may be less vulnerable to the effects of stress, as indicated by studies where abuse was associated with reduced hippocampal volume and hippocampal-dependent memory performance in males but not in females (e.g. Samplin et al., 2013; Frodl et al., 2010; Shansky et al., 2010). Females also show differences in prefrontal cortex and amygdala circuitry, manifesting as a stress-sensitivity that may partly explain the larger proportion of women who are diagnosed with MDD (Shansky et al., 2010). Future work should aim to further disentangle the varying cognitive profiles associated with early adversity across genders.

Additional confounds of our analyses include stress exposure after childhood as well as individual dispositions and external sources contributing to resilience. In contrast to the current findings, certain observations suggest the potential for a pro-resilience effect of moderate levels of stress, and specifically, that enduring stress may promote a sense of mastery. In animal studies, research on stress inoculation suggests that exposure to early stress is associated with more effective responses in future stressful circumstances (Russo, Murrough, Han, Charney, & Nestler, 2012). Other work proposes that the relationship between stress and many behavioural domains can be described as an inverted U-shape curve, with low and high stress impairing behaviour, but moderate levels promoting positive coping responses (McEwen & Gianaros, 2011). Future research should clarify how stress in adulthood, whether chronic, moderate, or

momentary, may additionally explain differences in cognitive performance. At the same time, social support, healthy relationships, spirituality, and finding meaning in life have proven to be protective against allostatic load and neurocognitive decline (Juster, McEwen, & Lupien, 2010). Prospective work on the relationship between early adversity and cognition should also consider protective factors so that we may harness mechanisms of resilience in preventative and restorative practice.

Lastly, our use of two samples which received different variants of cognitive remediation may have added error variance to our results. More rigorous methodology would examine treatment response with a consistent sample and treatment design, and may also include additional measures of executive functioning and everyday functional skills as part of the pre- and post- assessment batteries. In addition, refined measures of age of onset and number of episodes would be helpful to ensure the validity of results. A longitudinal approach would be ideal for providing empirical support for the causal association between childhood trauma and cognitive impairment in adulthood, as well as the associated perpetuating and attenuating factors.

Implications

The observations of the current study align with previous neuroimaging research to support a unique cognitive phenotype of individuals with a history of childhood adversity. Compared to less severely maltreated people, individuals who experienced higher levels of adversity demonstrate distinct neurocognitive features that appear to be associated with functional competence. Findings from previous studies on neurocognition in MDD may have been confounded by childhood adversity, a variable that emerges as a prepotent factor associated with impairment and that may potentially play a critical role in the widely accepted

association between cognition and functional skills. Future research on depression, cognition, and associated areas of functioning must account for childhood adversity to ensure a well-informed understanding of the complex interconnection of these variables. In addition, characteristics of non-maltreated individuals with MDD should be investigated to enhance our understanding of differing expressions of illness. Our findings may also extend beyond the diagnosis of MDD and have implications for clinical work and research among individuals with post-traumatic stress disorder, borderline personality disorder, and schizophrenia, to name a few, which are similarly marked by cognitive impairment and demonstrate strong associations with childhood trauma. In this view, childhood adversity is an imperative transdiagnostic variable and the consequences of which are important to address irrespective of diagnosis.

Additionally, our results reinforce the need to amplify current efforts of early intervention and refine treatments that will relieve consequences of adversity and foster resilience. Among these treatments, cognitive remediation offers a promising means of rebuilding cognitive skills and promoting new learning, and may be valuable for survivors of adversity regardless of their diagnosis. According to the current analysis, hippocampal-dependent cognitive facilities as well as neurocognitive processing speed are especially in need of remediation. Treating cognitive deficits among these individuals may also be important for targeting diminished functioning.

In conclusion, cognitive impairment among individuals with MDD is robustly associated with childhood adversity, yet these deficits remain responsive to cognitive remediation. Results emphasize the climate of childhood years as a critical element to address in clinical treatment and research.

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Appendix A

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

July 18, 2018

Ms. Melinda Kinney Department of Psychology Queen's University

ROMEO/TRAQ: #6024068
Department Code: PSYC-211-18
Study Title: Cognition and Functioning in Major Depressive Disorder: The Association Between Early Life Trauma, Impairment, and Response to Cognitive Remediation Treatment Co-Investigators: Dr. C. Bowie
Review Type: Delegated
Date Ethics Clearance Issued: July 18, 2018
Ethics Clearance Expiry Date: July 18, 2019

Dear Ms. Kinney,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Protocol – June 24, 2018
- Interview Guide – Childhood Experience of Care and Abuse (CECA)
- Interview Guide – LIFE
- Telephone Recruitment Script
- Letter of Information/Consent Form – Version 2 – July 16, 2018

Documents Acknowledged:

CORE Certificate – M. Kinney

Amendments: No deviations from, or changes to the protocol should be initiated without prior written clearance of an appropriate amendment from the HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

Renewals: Prior to the expiration of your ethics clearance you will be reminded to submit your renewal report through ROMEO. Any lapses in ethical clearance will be documented on the renewal form.

Completion/Termination: The HSREB must be notified of the completion or termination of this study through the completion of a renewal report in ROMEO.

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events

must be reported within 15 days after becoming aware of the information.

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint.

Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete.

Yours sincerely,

Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.