EXECUTIVE FUNCTIONING AND ANTERIOR CINGULATE CORTEX VOLUME AS POTENTIAL MODERATORS OF THE COMBAT EXPOSURE-PTSD RELATIONSHIP

by

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ABSTRACT

LENA ETZEL. Executive Functioning and Anterior Cingulate Cortex Volume as Potential Moderators of the Combat Exposure-PTSD Relationship.
(Under the direction of DR. JENNIFER B. WEBB and DR. GEORGE J. DEMAKIS)

Combat, a common source of trauma in the military, is consistently predictive of post-traumatic stress disorder (PTSD) among servicemembers deployed to Iraq and Afghanistan. PTSD has detrimental effects on post-deployment health and psychosocial functioning. The cognitive model of PTSD posits that automatic threat appraisals maintain PTSD when they generalize to safe situations. As a result, the ability to modify this automatic response may support re-adaptation to the civilian context following deployment. Executive functioning (EF) includes suppressing automatic, incorrect responses (inhibition), generating and holding on to alternative, more context-appropriate perspectives (working memory), and flexibly shifting toward them (cognitive flexibility) and may act as a buffer by enabling re-consideration of trauma appraisals that otherwise maintain the combat exposure-PTSD relationship. Additionally, the anterior cingulate cortex (ACC), a brain region within the ventromedial prefrontal cortex, supports decision-making in uncertain contexts, regulating emotion to prevent incorrect automatic threat responses. Consequently, a smaller ACC volume may be associated with a diminished ability to adjust incorrect automatic threat appraisals. Using data from the Chronic Effects of Neurotrauma Consortium Study 34 (CENC-34) examining health outcomes following combat exposure and neurotrauma, the present study examined the factor structure of EF, and examined the resulting EF components and ACC volume as moderators in the relationship between combat exposure and PTSD, including PTSD symptom severity as well as diagnostic status. Participants were Iraq and Afghanistan Veterans ($N = 241$) who passed performance and symptom validity thresholds. Factor analysis of EF tests yielded two components, Cognitive Flexibility and Working Memory. After

adjusting for age, sex, years of education, time since trauma, current Major Depressive Disorder (MDD) diagnosis, and presence of deployment mTBI, EF components were not associated with PTSD symptoms or diagnosis, and no support was found for an interaction between either component and combat exposure. In these models, combat exposure was significantly associated with PTSD symptoms and PTSD diagnosis. Similarly, after adjusting for age, current MDD diagnosis, presence of deployment mTBI, and total intracranial volume, combat exposure and ACC volume were not associated with PTSD symptoms or diagnosis and results did not support an interaction effect between combat exposure and ACC volume. Unexpectedly, across all models, current MDD diagnosis was the most consistently predictive of PTSD symptoms and PTSD diagnostic status. The present work was an initial foray toward advancing theoretical, empirical, and clinical understandings of the factors contributing to persistent PTSD in Veterans. Our replication of the association between MDD and PTSD underscores the need to comprehensively assess for relevant comorbidities in clinical settings. Additionally, with combat exposure as a significant predictor of PTSD symptom severity, individuals exposed to combat may benefit from periodic screenings to enable early detection and intervention.

Keywords: Veterans, combat exposure, PTSD, anterior cingulate cortex, executive functioning

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DEDICATION

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ACC	Anterior Cingulate Cortex
AR	Arithmetic
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CF	Cognitive Flexibility
dACC	Dorsal Anterior Cingulate Cortex
DRRI-2	Deployment Risk and Resilience Inventory-2 Combat Exposure
DS	Digit Span
FAS	FAS Controlled Oral Word Association Test - Letter Fluency
INH	Inhibition
LNS	Letter Number Sequencing
MDD	Major Depressive Disorder
mTBI	Mild Traumatic Brain Injury
MR	Matrix Reasoning
PTSD	Post-Traumatic Stress Disorder
rACC	Rostral Anterior Cingulate Cortex
SIM	Similarities
TMTB	Trail Making Test Part B
vmPFC	Ventromedial Prefrontal Cortex
VHA	Veterans Health Administration
VP	Visual Puzzles
WAIS-IV	Wechsler Adult Intelligence Scale-IV
WM	Working Memory

CHAPTER 1: INTRODUCTION

Over 1.9 million Veterans have served in the post-9/11 conflicts, and many experience poor health following these deployments (Institute of Medicine, 2013). Service members returning from Iraq and Afghanistan conflicts are more likely to have deployed more times, for longer periods of time, and with shorter periods between deployments (Institute of Medicine, 2013). As medical treatment and protective body armor have continued to advance, Veterans are more likely to survive compared to individuals deployed during previous wars (Church, 2009). Yet, these increased survival rates do not mean Veterans and service members are unaffected: they are still at risk for a host of health challenges during and following their deployment. Post-traumatic stress disorder (PTSD) and mild traumatic brain injuries (mTBI), the "signature injuries" of the Iraq and Afghanistan conflicts, are among the primary reasons for post-9/11 Veterans seeking care at Veterans Health Administration (VHA) clinics (see in Brancu et al., 2017). PTSD has wide-ranging and deleterious impacts on occupational and social functioning, necessitating short- or long-term disability and contributing to relational distress (Galovski & Lyons, 2004). As a result, efforts to better understand factors influencing post-deployment mental health have become a key focus for improving long-term Veteran health.

A common form of trauma among Veterans involves exposure to combat while deployed. In combat, perceptions of threat and associated habitual responses are required for safety and survival. The cognitive model of PTSD posits that persistent and automatic threat appraisals are important contributors to the maintenance of symptoms after trauma exposure (Ehlers & Clark, 2000). Specifically, according to the cognitive model of PTSD, PTSD describes the persistence of these responses despite changes in context, such as the transition to civilian life post-combat. Informed by the model, cognitive resources which support the modification of default responses

in favor of new information may be important when seeking to understand the relationship between prior combat exposure and current PTSD. While many factors are known to influence adaptation to the civilian environment following deployment, including unit cohesion (Campbell-Sills et al., 2020) and perceived social support (Jukić et al., 2020; Proescher et al., 2022), the cognitive model of PTSD (Ehlers and Clark, 2000) positions cognition as an important factor in the maintenance of PTSD to inform targets for intervention. Below, executive functioning (EF), as well as anterior cingulate cortex volume (ACC), are briefly introduced as potential influences on PTSD symptoms and/or diagnostic status among Veterans following exposure to combat.

First, EF refers to a family of cognitive abilities that enables individuals to flexibly respond to changes in environmental demands (Jurado & Rosselli, 2007). Specifically, according to the unity/diversity model of EF, the ability to suppress automatic responses (inhibition), shift toward alternative responses (cognitive flexibility), and actively maintain relevant representations or information (working memory) are thought to be manifestations of EF that work interdependently as well as independently (Miyake et al., 2000). In the context of the cognitive model of PTSD (Ehlers & Clark, 2000), EF may support individuals in adjusting their trauma-informed threat appraisals that are posited to maintain their PTSD following combat exposure. However, inconsistencies in prior work call for a more nuanced examination of EF in PTSD by assessing the role of individual components. Specifically, components of EF such as inhibition, cognitive flexibility, or working memory may support adaptation to the civilian environment in different ways, by modifying the relationship between prior combat exposure severity and current PTSD.

Functional neuroimaging work has supported interdependence among key brain regions, most commonly the amygdala, the hippocampus, and the ventromedial prefrontal cortex (vmPFC), which includes the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) among other areas (Hughes & Shin, 2011; Rauch et al., 2006; Shin et al., 2005, 2006). Organized within the neurocircuitry model of PTSD (Rauch et al., 1998), the vmPFC is thought to regulate the fear-response of the amygdala. Specific regions within the vmPFC, such as the ACC, are thought to downregulate automatic threat responses and promote selection of appropriate responses in non-threatening situations. Yet, prior clinically-oriented research has focused primarily on broader regions such as the vmPFC or even the PFC most broadly, suggesting the need to integrate findings from cognitive psychology, experimental paradigms, and neuroscience to advance our understanding of the regions within the vmPFC most relevant to the regulation of the threat response.

Specifically, the conflict monitoring hypothesis (Botvinick et al., 2001, 2004) suggests that the ACC is a key site for detecting changes in situational demands (Shackman et al., 2011). Notably, as posited by the neurocircuitry model of PTSD (Rauch et al., 1998), a single brain region is unlikely to occupy an exclusive role in PTSD persistence, and as such, the ACC is examined here as part of a larger cognitive activation network relevant to threat detection/evaluation and response selection. As suggested by the cognitive model of PTSD, conflict detection is likely an important skill to differentiate between combat and non-combat contexts, to prevent threat responses (e.g., hypervigilance) from occurring in non-threatening situations, a defining feature of PTSD. Functional MRI studies have demonstrated associations between activity in the ACC and emotion regulation learning in novel contexts (Zweerings et al., 2018), and previous work has established consistent correspondence between regional brain

activity and volume (Qing & Gong, 2016). Those with lower ACC volume may be slower to recognize that a situation in civilian life has different response requirements than those in combat, which may contribute to longer-term maintenance of threat responses outside of combat (e.g., Carter & van Veen, 2007; Maier & di Pellegrino, 2012). In turn, persistent threat responses to non-threatening situations can become life-interfering, resulting in their identification as PTSD symptoms.

Typically, PTSD is diagnosed when symptoms surpass pre-defined thresholds of severity, frequency, and duration (American Psychiatric Association, 2013). Yet, some work suggests that PTSD is best reflected as one extreme of a continuum of symptom severity (Ruscio et al., 2002). Those with subthreshold symptoms may also experience functional impairment (Pietrzak et al., 2009) and thus may benefit from treatment (Dickstein et al., 2013). Because much research focuses on diagnostic group-level comparisons (e.g., O'Doherty et al., 2015; Polak et al., 2012), individuals with varying levels of subthreshold PTSD symptoms may be grouped together, obscuring important intra-group variability. Examination of factors influencing PTSD symptom severity has the potential to yield important insights regarding the cognitive processes relevant to symptom maintenance in subthreshold PTSD.

In sum, the present study examined the extent to which EF components and ACC volume each modified the relationship between past combat exposure and current PTSD symptom severity or diagnostic status, in Iraq and Afghanistan combat Veterans. The subsequent sections will include a thorough review of relevant theoretical and empirical work.

CHAPTER 2: LITERATURE REVIEW

2.1 HEALTH AND PSYCHOSOCIAL CORRELATES OF PTSD

PTSD has detrimental effects on individuals, their social environment, and society at large. Namely, PTSD carries a large economic burden due to the high healthcare costs, averaging around $24,000 per person per year (Bilmes, 2021; von der Warth et al., 2020). It also contributes to disruptions in occupational functioning, including short- and long-term disability, as well as familial and relational distress (Galovski & Lyons, 2004). First and secondhand accounts (e.g., from caregivers) about the experience of PTSD highlight social isolation, emotional reactivity, and the sense of feeling trapped in the past (Eubanks, 2022).

A diagnosis of PTSD requires a traumatic event, as well as the presence of symptoms across four "symptom clusters", including intrusion symptoms (i.e., recurrent, involuntary, and intrusive recollections of the traumatic event), avoidance (i.e., persistent avoidance of internal experiences or external reminders), negative alterations in mood and cognition (i.e., negative emotional states, anhedonia, negative beliefs about the self and others), and alterations in arousal and reactivity (i.e., hypervigilance, heightened startle response; American Psychiatric Association, 2013). Additionally, symptoms must have persisted for more than one month and caused impairment or distress in multiple areas such as social and occupational functioning. Traumatic events may include combat exposure as a combatant or civilian, threatened or actual physical assault, threatened or actual sexual violence, accidents, or natural disasters. The current "gold standard" of measurement for quantifying PTSD symptoms for a diagnosis is the Clinician Administered PTSD Scale, or the CAPS-5 (DSM-5 criteria for PTSD), a rigorously developed and tested structured interview schedule (Weathers et al., 2018). It incorporates both frequency

and intensity when qualifying the severity of symptoms, and requires a specific severity threshold in order to count a given symptom as present to make the diagnosis.

Importantly, recognition of the impact of the trauma may be limited for those without an official diagnosis of PTSD, and may also restrict their access to trauma treatment. Yet, along the spectrum from subsyndromal symptoms to full-threshold diagnosis, PTSD is associated with a range of outcomes indicative of poor health, well-being, and quality of life. Specifically, even those with subsyndromal PTSD experience worse health and psychosocial difficulties compared to those without any symptoms, including interpersonal and financial difficulties, job dissatisfaction, more frequent medical visits and worse self-reported health (Bryan et al., 2014; Pietrzak et al., 2009). Individuals with full-threshold as well as those with subsyndromal PTSD are also at elevated risk of developing sleep and respiratory conditions (El-Gabalawy et al., 2018). Taken together, PTSD has negative effects on individuals along the symptom continuum.

2.2 PTSD IN THE US VETERAN POPULATION

PTSD is prevalent among Veterans exposed to combat (Thomas et al., 2017). Iraq and Afghanistan Veterans diagnosed with PTSD have reported poor physical health outcomes such as chronic pain (Fishbain et al., 2017), as well as high levels of suicidal ideation (Ramchand et al., 2015). Similarly, according to data from the National Health and Resilience in Veterans Study, PTSD among U.S. Veterans was associated with an increased risk for several psychiatric conditions (e.g., mood and substance use disorders) and suicidality (Wisco et al., 2014). Nearly a quarter of Iraq and Afghanistan Veterans (Fulton et al., 2015) and over half of Veterans receiving care at a VHA clinic have a PTSD diagnosis (see in Brancu et al., 2017).

2.3 COMBAT EXPOSURE AND PTSD

Combat exposure is a common source of trauma for deployed servicemembers and is consistently predictive of PTSD among service members deployed to Iraq and Afghanistan (Ramchand et al., 2010, 2015). Combat is a context in which perceptions of threat are required for safety and survival. Repeated exposure to combat, casualties, and other violent or dangerous circumstances might further solidify threat appraisals. While these may represent normative shifts in thinking during and immediately following trauma exposure, solidified threat appraisals may be resistant to changes in context, which may result in continued threat perceptions even in typically non-threatening situations. Combat exposure may be quantified in a variety of ways, including a number or percentage of experiences, the types of experiences, and/or the duration of experience(s) (e.g., Keane et al., 1989; Vogt et al., 2013). Importantly, combat exposure is associated with a threefold increase in new onset self-reported PTSD symptoms (T. C. Smith et al., 2008), yet only a fraction of those exposed to combat develop persistent, interfering symptoms, and even fewer are diagnosed with PTSD.

2.4 PTSD AS A DISTINCT CLINICAL SYNDROME…?

Despite the presence of specific criteria, diagnosing PTSD remains a challenging process. The presence of a distinct clinical syndrome is typically characterized by its association with a known genetic or biological etiology, such as a positive blood test (Broman-Fulks et al., 2006). In the case of PTSD (per DSM-5; American Psychiatric Association, 2013), a distinct “index” trauma, or a traumatic event that precedes the onset of symptoms, is required. Yet, the impact of this experience demonstrates considerable variability as a result of multiple factors such as prior trauma history, personality, coping, cognition, and access to resources, suggesting a so-called nontaxonic (i.e., additive or graded) etiology. Indeed, a taxometric analysis of PTSD suggested

that rather than being a distinct clinical syndrome, it reflects the upper end of a post-trauma symptom continuum (Ruscio et al., 2002). Accordingly, PTSD symptoms may still be present and cause distress even though an individual may not meet the diagnostic threshold (Broman-Fulks et al., 2006).

This "subsyndromal" PTSD is captured by the Clinician Administered PTSD Scale (CAPS-5; Weathers et al., 2018) under the "symptom severity score," which positions individuals along a continuum that reflects the cumulative severity of clinician-assessed symptoms. In healthcare contexts, symptom continua are often dichotomized to delineate who does and does not qualify for services, treatment, and benefits. The utility of diagnostic frameworks may lie in their ability to simplify resource allocation by identifying those who may have the greatest need for intervention. Although routing those with a diagnosis to treatment seems appropriate given their likely higher average symptom severity (Ruscio et al., 2002) and hence, their greater need for treatment, little if any information exists regarding the utility of treatment for individuals whose symptom severity and breadth remains below the diagnostic threshold. Indeed, considering individuals with subsyndromal PTSD within the "no diagnosis" group may mask important within-group variability as well as between-group similarities. Consistent with this notion, prior work indicated that over a third of those with subsyndromal PTSD converted to a diagnosis one year later (Fink et al., 2018). This suggests that the risk and resilience factors relevant for symptom maintenance remain important across the diagnostic divide.

2.5 THEORETICAL BACKGROUND: THE COGNITIVE MODEL OF PTSD

The cognitive model of PTSD describes the maintenance of symptoms as resulting in part from "default appraisals" developed in the trauma context (Ehlers & Clark, 2000).

Generalization of trauma-informed appraisals and personalization of appraisals is also common (e.g., “I attract bad things”), which may prevent recognition that the trauma is situation-specific (e.g., “That was dangerous but I am safe now”). Negative appraisals may also be associated with trauma sequelae, contributing to persistent negative beliefs about the self (e.g., interpreting symptoms or changes in social/occupational functioning as indicators of permanent damage) and others (e.g., perceiving others’ reactions as judgmental). According to the model, these trauma-informed beliefs are thought to persist and become inflexible, creating a recurrent sense of threat and an associated default response even outside of the trauma context. In a non-combat context, such automatic responding is no longer adaptive as it undermines or prevents the generation of non-threatening interpretations that support flexible problem-solving approaches. As a result, persistent, inflexible automatic threat appraisals are thought to contribute to the maintenance of PTSD.

The cognitive model might be best illustrated with the use of an example. In a relatively benign situation such as an amusement park, loud noises and screaming may be common. However, for individuals with prior combat exposure, such sounds may signal danger, resulting in default threat-associated physiological (e.g., hyperarousal), affective (e.g., fear), and cognitive (e.g., “something bad is happening”) responses. Consequently, appraisals which may have initially carried survival-supporting value in wartime now contribute to the person relating to their trauma and its sequelae in ways that promote a chronic sense of threat.

2.6 TREATMENT CONSIDERATIONS

Consistent with the centrality of inflexible threat appraisals to the cognitive model of PTSD, Veterans diagnosed with combat-related PTSD are commonly referred for Cognitive Processing Therapy (CPT), a manualized treatment that encourages the reconceptualization of

traumatic experiences through cognitive restructuring of trauma-informed beliefs (Resick et al., 2016). CPT has decades of empirical support and widespread use in a variety of contexts (Asmundson et al., 2019). The VHA has identified CPT as one of four treatments with strong research support for treating PTSD (Department of Veterans Affairs & Department of Defense, 2017). Specifically, individuals learn to challenge and modify their inflexible threat appraisals or "stuck points" (e.g., "I cannot trust anyone") that are thought to pose a barrier to their reintegration into non-combat settings (Resick et al., 2016). Because CPT involves cognitive restructuring of the trauma-informed beliefs, it also requires cognitive distance from one's default perspective to modify it using new or alternative information. As such, cognitive abilities that support this restructuring process by facilitating the consideration and use of alternative information seem crucial.

2.7 EXECUTIVE FUNCTIONING AS ADAPTIVE BEHAVIOR

Executive functioning (EF) refers to a class of complex, interrelated cognitive abilities that enable individuals to generate, consider, and flexibly select from multiple alternatives in a given situation (Aupperle et al., 2012; Jurado & Rosselli, 2007). As such, EF is thought to be a key facilitator of adaptation to novel or unfamiliar demands (Aupperle et al., 2012). The conceptualization of EF has been the subject of much debate, with scholars having divergent views regarding the nature of the construct and the types of cognitive abilities that should be included under the larger executive functioning umbrella (Baggetta & Alexander, 2016; Karr et al., 2018).

In brief, early approaches to the conceptualization of EF centered primarily on its role in *how* behavior is initiated and controlled (Baddeley & Hitch, 1974; Lezak, 1983; Norman & Shallice, 1986; Stuss & Benson, 1986). For example, according to Lezak (1983), EF is composed

of multiple parts, including the ability to formulate and plan a goal, and to carry out the goal-directed plan in an effective manner. A similar sequential framework has been put forth by Zelazo et al. (1997), who suggested the presence of four components that support problem solving, including problem representation, planning, execution, and evaluation. A hierarchical cognitive model has also been proposed that suggests the presence of a "central executive" that controls and regulates lower-level cognitive processes (e.g., Baddeley & Hitch, 1974; Norman & Shallice, 1986). Additionally, much of the early study of EF was informed by human lesion studies of the frontal lobe (Stuss & Benson, 1986; Szczepanski & Knight, 2014), which was classically thought to be the seat of most if not all higher-order cognitive processes (Luria, 1973, 1976). Even though empirical work on EF is characterized by some inconsistencies regarding the specific abilities that constitute it, there appears to be widespread recognition of the complexity and relevance of EF to adaptive human behavior (Jurado & Rosselli, 2007).

2.7.1 FACTOR STRUCTURE OF EXECUTIVE FUNCTIONING

Over the last two decades, much of the field has centered around the unity/diversity model of EF, as measured by performance on cognitive/neuropsychological tests (Miyake et al., 2000; initially coined by Teuber, 1972). Based on Miyake and colleagues' influential work using a latent analytic approach, EF is composed of three separable components: shifting/flexibility, updating, and inhibition, which are thought to represent the "diversity" of EF skills. At the same time, these skills are also thought to be interrelated with underlying commonality, reflecting their "unity." Diamond's model of EF (2013) also centers around three core interdependent EF abilities, including updating/working memory (i.e., holding information in mind and mentally manipulating it), inhibition (i.e., suppressing an automatic response when attending to a stimulus or performing a task), and set-shifting/cognitive flexibility (i.e., flexibly modifying one's

response in the context of changing demands), which are thought to interact to support more complex EF such as planning or reasoning. As noted above, prior work based on these models has used cognitive/neuropsychological testing to quantify their components, yet because they are primarily conceptual frameworks, the components described within the models are not linked with any specific measures or neuropsychological/cognitive tests.

To better understand the possible unity/diversity of EF, previous research has turned to factor analysis in an attempt to accurately and parsimoniously represent its structure. Multidimensional models have the advantage of capturing distinct yet related executive functions which allows for the examination of more nuanced relationships. Yet, a unidimensional factor provides the benefit of increased reliability due to increased stability and construct coverage with more tests as well as the ability to examine the variance common to multiple EF tasks (i.e., unity of executive functioning; Snyder et al., 2015). In sum, a factor structure of EF should strike a balance between parsimony and explanatory value.

Across studies, the three-factor structure (Miyake et al., 2000) has become the most frequently studied approach when seeking to conceptualize EF (Karr et al., 2018). Yet, Karr and colleagues (2018) point out that their meta-analysis revealed a great variety of potential measurement models for EF, including two-factor models, three-factor models, and unidimensional models. Importantly, model selection was variable and highly context-dependent across studies, suggesting that EF may not necessarily evidence the same factor structure in each setting, population, or set of tests. These inconsistencies in factor structure and thus, in the conceptualization of EF, may be further complicated by the "task impurity" problem (Snyder et al., 2015). The "task impurity problem" posits that many different executive and non-executive abilities interact to support performance on tests commonly used in neuropsychological practice

and research (e.g., color processing speed and speaking rate in the Stroop task; Snyder et al., 2015). Consequently, this underscores the importance of establishing an EF structure when examined in each new population and with any given set of measures.

Snyder and colleagues (2015) recommend that research seeking to examine EF and by extension, its components, should incorporate multiple measures with different task demands (e.g., timed and untimed tests, visual and verbal and motor tests) so that the convergence or shared variance across these tests has the greatest likelihood of reflecting an overarching construct. In contrast to more "pure" cognitive psychological tasks used in experimental work (e.g., N Back test as used in work by Miyake et al., 2000) which may be more oriented toward delineation of individual cognitive skills, many commonly used neuropsychological tests generally require more than one cognitive skill to perform adequately (e.g., Wisconsin Card Sorting Test). Consequently, tasks measuring cognitive flexibility (also referred to as set shifting, shifting, and flexibility) often require inhibitory control, which has also been characterized as a critical component of cognitive flexibility (e.g., Diamond, 2013; Monsell, 2003). For example, Bettcher et al. (2016) tested competing models of their EF tasks, examining a three-factor, two-factor, and unidimensional factor structure in a sample of community-dwelling older civilians. Factor analyses revealed a high correlation (r = .97) between the shifting (i.e., flexibility) and inhibition factors, resulting in the authors retaining the two-factor solution (i.e., set-shifting/inhibition and working memory).

Accordingly, informed by prior investigations of the factor structure of EF (e.g., Bettcher et al., 2016; Johnco et al., 2015; Karr et al., 2018), we propose to test for the presence of one or more latent EF component factors (e.g., Cognitive Flexibility, Working Memory, Inhibition) using an exploratory factor analysis, and hypothesize that two distinct factors, Cognitive

Flexibility/Inhibition and Working Memory, will be the best fitting and most parsimonious model in comparison to one-factor and three-factor models, by striking a balance between "unity" and "diversity" (Aim 1).

2.7.2 EXECUTIVE FUNCTIONING AND PTSD

Informed by the cognitive model of PTSD (Ehlers & Clark, 2000), threat appraisals are initially adaptive responses that arise in response to traumatic situations such as combat to support survival. However, when these threat appraisals become the default and occur even in non-threatening situations, they become maladaptive and harmful, potentially resulting in the clinical syndrome of PTSD. In theory, this self-maintaining cycle can be interrupted if individuals recognize when an automatic thought process does not match the context. They can then generate and flexibly select an appraisal appropriate to the context. Thus, as a higher-order cognitive function involving the management of thought processes, EF is likely instrumental to adaptation, as would be required following a change in context or environmental demands. Consistent with the notion that persistent PTSD symptoms denote difficulty adjusting to non-combat environments, meta-analytic work has demonstrated group-level differences in EF between mixed-trauma adult (small to medium effect size; Polak et al., 2012; Scott et al., 2015; Woon et al., 2017) and older adult samples diagnosed with PTSD (large effect size; Schuitevoerder et al., 2013) compared to trauma-exposed controls without PTSD and healthy controls. For example, reviews of the literature indicate that individuals diagnosed with PTSD performed worse on EF measures such as Trail Making Test B, Wisconsin Card Sorting Test (perseverative errors), Wechsler Adult Intelligence Scale-IV Digit Span, or Stroop interference compared to trauma-exposed or healthy controls (Polak et al., 2012; Schuitevoerder et al., 2013). These findings indicate that EF is a potential protective factor, or conversely, that EF deficits

represent a vulnerability factor for the maintenance of PTSD (Aupperle, 2012; Polak et al., 2012). Moreover, as not all combat-exposed individuals develop the same severity of PTSD symptoms or receive the diagnosis, EF abilities may modify the relationship between combat exposure and PTSD.

However, prior work has inconsistently included a wide variety of tests thought to measure EF, either within composites or as individual scores, creating confusion about what *does* and what *does not* constitute "executive functioning." In a sample of US male Marines, pre-deployment EF (assessed using a composite consisting of a continuous performance test, an n-back test, and a Go/NoGo paradigm) predicted post-deployment CAPS symptom severity score (Liu et al., 2023); however, the composite did not moderate the relationship between combat exposure and PTSD symptom severity (with CAPS). In our own work with a sample of Iraq and Afghanistan combat veterans, an EF composite (using Trail Making Test B, Wisconsin Card Sorting Test (perseverative errors), Wechsler Adult Intelligence Scale-IV Similarities, and Stroop interference) did not moderate the relationship between past combat exposure and self-reported PTSD symptom clusters (Etzel et al., 2024). Systematic, theory-driven selection of EF measurements and analytically sound dimension reduction are necessary to permit reliable and valid inferences regarding the role of EF.

2.7.3 EXECUTIVE FUNCTIONING COMPONENTS AS MODERATORS

Emerging work has begun to examine specific components of EF, measured either by individual cognitive/neuropsychological test performance, or performance summarized across a small number of tests within a subdomain (i.e., inhibition, cognitive flexibility, working memory), with the goal of clarifying some of the discrepant findings observed when EF is considered as unidimensional.

Some research has observed that individuals with military service-associated PTSD exhibit working memory deficits on single tasks relative to healthy controls (Nejati et al., 2018) and relative to military personnel without PTSD (Russell & Mussap, 2023). In a meta-analysis, Scott et al. (2015) also found working memory to be associated with PTSD among both civilian and military samples. However, when symptoms were viewed on a continuum, working memory, measured by single task performance, did not predict self-reported PCL scores (across diagnostic status; DeGutis et al., 2015; Mathew et al., 2022).

Similar work has observed links between inhibition skills and PTSD diagnostic status. Iraq and Afghanistan Veterans diagnosed with PTSD also presented with more difficulties inhibiting motor responses and committed more errors compared to controls (Swick et al., 2012). Interestingly, inhibition was also previously observed to account for a substantial proportion of variance in PCL scores among Iraq and Afghanistan Veterans independent of diagnostic status (DeGutis et al., 2015), though another study found no association between inhibition skills (measured with a single task) and CAPS symptom severity (Aase et al., 2017).

Finally, a small body of work has documented inverse associations between cognitive flexibility and PTSD symptoms. Performance on a single task of cognitive flexibility was associated with significantly less severe PTSD symptoms (on the CAPS) after 13 months in an adult sample of mixed-trauma survivors (Ben-Zion et al., 2018). In a U.S. military context, combat-exposed servicemembers with more severe self-reported PTSD symptoms on the PCL-5 demonstrated slowed reaction time with residual interference from prior trials on a task-switching paradigm, suggestive of difficulties with cognitive flexibility (Popescu et al., 2022).

Though marked by some inconsistencies depending on the specific EF tests within each domain and the metric of the outcome (e.g., self-report versus clinician interview of PTSD

symptoms; PTSD symptom continuum vs. formal diagnosis), the EF components proposed by Miyake et al. (2000) remain a relevant and important consideration for depicting the relationship between combat exposure and PTSD, when situated in the context of the cognitive model of PTSD. Specifically, the ability to suppress automatic combat-informed beliefs, generate alternative, more context-appropriate perspectives, and flexibly shift toward them, all of which are considered components of EF (Miyake et al., 2000), may reduce the effect of combat exposure on persistent PTSD. In their recent work, Liu and colleagues (2023) called for continued study of the specific role of EF components within the relationship between combat exposure and PTSD. Thus, we propose to test each identified component of EF (see Aim 1) as a moderator of the relationship between combat exposure and PTSD (reflected in separate models as PTSD symptom severity and PTSD diagnostic status; Aim 2a).

2.8 ANTERIOR CINGULATE CORTEX VOLUME AS A MODERATOR

Much of human behavior is automatic or habitual, which allows for the optimal use of limited cognitive resources and efficient responding to environmental demands. However, the brain must also detect when changes in the environment suggest that automatic or habitual responses are no longer optimal (Mansouri et al., 2009). Understood in the context of the cognitive model of PTSD, difficulties detecting changes in the environment may result in the persistence of outdated combat-informed appraisals or responses that are misaligned with the civilian context. In addition to performance on standardized testing, research has also examined the role of neural structures that are involved in regulating emotion in potentially threatening situations to enable accurate assessment and flexible responses in new or different situations.

The neurocircuitry model of PTSD (Rauch et al., 1998) posits that the interplay of several brain regions, including the vmPFC, hippocampus, and amygdala, contribute to an overactive

threat response (i.e., otherwise known as PTSD). Aligned with this model, within the vmPFC (i.e., orbitofrontal cortex, ACC, medical prefrontal cortex), the ACC is thought to support decision-making particularly in uncertain or risky contexts such as when a new situation appears similar to a prior traumatic experience (Botvinick et al., 2001, 2004). More specifically, the ACC is thought to be a part of a cognitive activation network that helps detect a change in environmental demands to inform the most appropriate course of action.

According to the *conflict monitoring hypothesis* (Botvinick et al., 2001, 2004), the ACC is thought to be a central driver of this process because it uses environmental information to detect dissimilarity between external information and internal default appraisals. When the ACC detects a mismatch, it updates the set of rules that determine how to behaviorally respond to a given situation (Botvinick et al., 2001; Hyafil et al., 2009). Consequently, the ACC helps individuals adapt to change, which is particularly relevant for potential threatening situations (Etkin et al., 2011) encountered by combat-exposed veterans after they return from deployment.

Of note, different parts of the ACC are thought to work together to detect and adapt to situations with conflicting information. The dorsal ACC (dACC) is involved in the general detection of conflicting information in the environment, whereas the rostral ACC (rACC) seems to be selectively activated to support adaptation in *emotional* situations with conflicting information (Maier & di Pellegrino, 2012). With practice, individuals with typically functioning ACC would be expected to ignore task-irrelevant information and attend to important information, even if task-irrelevant and relevant information are conflicting. Experimental research has demonstrated that with practice, healthy controls (no known brain damage) and those with non-ACC brain damage show improvements in speed of classifying emotional facial expressions when distractor text is inconsistent (i.e., the word “happy” superimposed on a sad

face). Individuals with rACC lesions are persistently slower to label emotions correctly when there is conflicting emotional information present even with practice, suggesting that individuals with lesions in the rACC have difficulty adapting to focus on a task when there are distractions in an emotional context (Maier & di Pellegrino, 2012). Similarly, compared to healthy controls, individuals with PTSD exhibited reduced rACC activity in response-conflict situations that involve emotional stimuli (Kim et al., 2008) which are a common proxy for threatening situations, consistent with the role of the ACC in self-regulation. In the PTSD group, ACC activity was also inversely associated with PTSD symptom severity.

In sum, functional neuroimaging work suggests that both major regions of the ACC (dACC, rACC) must be activated in order to effectively respond to emotional situations involving irrelevant, conflicting information. In addition, given the associations between ACC activation and PTSD, difficulties adapting to emotional tasks with incongruent emotional information may be relevant for real-world emotional situations with distracting and irrelevant PTSD symptom triggers. Structural neuroimaging research has observed similar associations between lower ACC volume and PTSD, suggesting that ACC volume may be an appropriate proxy for ACC activation.

Reduced ACC volume is thought to result in a lessened ability to inhibit an automatic threat response, even after repeated exposure to a non-threatening stimulus (Young et al., 2018). For example, in those with lower ACC volume, distracting threat perceptions (e.g., “all crowds are dangerous”) may conflict with and distract from non-threatening emotional situations (e.g., having fun in an amusement park), resulting in over-focus on the threat perception. Consequently, given the role of the ACC in adapting to and managing this response conflict,

slowed or absent ability to disregard the irrelevant threat perception may persist over time, contributing to maintenance of automatic threat appraisals and resultant distress (i.e., PTSD).

At a group-level, several meta-analyses have demonstrated reduced volume in mixed adult samples diagnosed with PTSD, primarily in comparison to trauma-exposed individuals without PTSD (Karl et al., 2006; Li et al., 2014; O'Doherty et al., 2015), and in comparison to individuals with no known trauma exposure (O'Doherty et al., 2015). However, comparisons are complicated by small sample sizes and the inconsistent divisions of the ACC used across studies (e.g., rostral/ventral, dorsal/caudal, subgenual, pregenual, left, right). For example, O'Doherty and colleagues (2015) report only left, right, and combined ACC comparisons, whereas Li et al. (2014) and Karl et al. (2006) report on findings at the level of the whole ACC. Overall, the emerging body of research examining ACC volume in the context of PTSD following combat exposure in Veterans remains somewhat small. As a result, it is difficult to draw specific conclusions regarding differences in the volume of particular sub-areas of the ACC between those diagnosed and not diagnosed with PTSD, and with non-trauma exposed individuals. Viewed more broadly across subdivisions of the ACC, combat-exposed Veterans with PTSD do generally demonstrate less volume in this key area of the brain associated with adaptation and downregulation of amygdala response (Woodward et al., 2006). Yet, some studies have also reported no difference in volume between combat-exposed Veterans with and without PTSD (Young et al., 2018) highlighting the need for continued region-level examination to build the literature base toward more reliable conclusions.

In sum, because EF components and ACC volume both support recognizing and responding to changes in situational demands, they may play unique roles in facilitating adaptation. As such, while prior combat exposure has demonstrated strong associations with

current PTSD (e.g., Liu et al., 2023; Ramchand et al., 2010), EF components and ACC represent two important indicators that may modify this relationship. Given the inconsistencies in ACC subdivisions noted above, the current state of the literature does not provide a strong research base to substantiate arguments regarding differential relationships with ACC subregions and PTSD; as such, whole bilateral ACC will be examined.

2.9 THE PRESENT STUDY

The present study examined the extent to which EF components and ACC volume modify the relationship between past combat exposure and current PTSD. As noted above, though frequently conceptualized as a dichotomy, PTSD likely reflects the upper end of a post-trauma symptom continuum rather than a distinct syndrome (Ruscio et al., 2002). Much published research to date focuses on group-level comparisons based on diagnostic categorization, which often inform recommendations for treatment and access to resources. Yet, post-trauma variability in symptoms captured by a continuous severity score may also be informative. Thus, an additional aim of the present analyses was to examine the hypothesized relationships for outcomes of PTSD symptom severity as well as PTSD diagnostic status.

As a precursor to testing the moderating role of EF components in the relationship between combat exposure and PTSD in US combat-exposed Veterans, we used factor analysis to examine relationships between neuropsychological test performance and the conceptually related yet empirically distinct components of EF: cognitive flexibility, inhibition, and working memory, all of which are thought to be highly relevant to the flexible modification of trauma-informed beliefs.

Study Aim 1. Examine and identify the best fitting factor structure of EF for this sample.

Hypothesis 1 (Figure 2)**:**

We hypothesized that the best fitting factor structure for the studied measures would be a correlated two-factor model. A two-factor structure of EF with cognitive flexibility (combined with inhibition) and working memory as separate latent factors was expected as informed by theoretical and empirical work.

Study Aim 2. Examine both EF components and bilateral ACC volume as moderators of the relationship between prior combat exposure and current PTSD symptom severity as well as PTSD diagnosis.

Hypothesis 2a:

Based on the above factor analysis, we hypothesized that EF components would moderate the relationship between combat exposure and current PTSD symptom severity such that the relationship between combat exposure and current PTSD symptom severity would be weaker at higher levels of EF.

Hypothesis 2b:

Based on the above factor analysis, we hypothesized that EF components would moderate the relationship between combat exposure and current PTSD diagnosis such that the relationship between combat exposure and likelihood of PTSD diagnosis would be weaker at higher levels of EF.

Hypothesis 3a:

We hypothesized that bilateral ACC volume would moderate the relationship between combat exposure and PTSD symptom severity such that the relationship would be weaker at larger, bilateral ACC volumes.

Hypothesis 3b:

We hypothesized that bilateral ACC volume would moderate the relationship between combat exposure and current PTSD diagnosis such that the relationship between combat exposure and likelihood of diagnosis would be weaker at larger, bilateral ACC volumes.

CHAPTER 3: METHODOLOGY

Data included in this study were collected as part of the Chronic Effects of Neurotrauma Consortium Study 34 (CENC-34) examining post-deployment mental health among Iraq and Afghanistan combat Veterans. All participants provided informed consent prior to participation. All procedures were approved by the Veterans Administration Institutional Review Board. The UNC Charlotte Institutional Review Board reviewed the procedures for this secondary analysis and approved it. All participants were compensated for travel and time at a rate of $150 for the Interview Visit (Visit 1) and $150 for the Neuroimaging Visit (Visit 2). Data were collected between February 2016 and March 2019. Due to data access and availability challenges, the study team discussed and implemented changes to the procedures to enable the analyses to be conducted while preserving the primary objectives. Appendix 1 contains a summary of changes that were made since the initial proposal of the project in August 2022.

3.1 PARTICIPANTS

A total of 342 participants completed the Interview Visit. Eligibility criteria for the study included at least one Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/ Operation New Dawn (OND) deployment with any report of combat exposure, ability to speak/read/write in English, a minimum age of 18, ability to comply with instructions to complete study tasks, and ability to provide informed consent. Exclusion criteria were a history of moderate or severe TBI, penetrating head injury, nonmilitary TBI with loss of consciousness, major neurologic disorder such as stroke, seizure, or spinal cord injury, and major psychiatric disorder such as bipolar disorder or schizophrenia. Individuals with current substance use disorder were also excluded. Of the 241 participants who passed performance and symptom validity thresholds, a total of 232 participants were invited to the Neuroimaging Visit. Due to the

neuroimaging procedures, pregnant individuals and individuals with ferrous metal other than fillings, including orthodontic devices or implanted objects known to generate magnetic fields (e.g., prosthetic devices, pacemakers, neurostimulators) were excluded from participating in the study.

3.2 PROCEDURE

A diagram depicting the participant flow through study stages is displayed in Figure 1. Potential participants were identified through the Veterans Integrated Services Network (VISN) 6 Mental Illness Research and Education Clinical Core (MIRECC) Post-Deployment Mental Health Data Repository (PDMH Data Repository, Durham VAMC IRB #01706) if they had agreed to be re-contacted for future data collection. A total of about 4000 Veterans were contacted by mail. Additional recruitment efforts included posting flyers across Hefner VAMC facilities, distributing brochures in waiting rooms, setting up recruitment tables in lobbies, and giving presentations at treatment team meetings so providers could identify any Veterans who may fit study criteria. A total of 803 individuals were screened and of those, 417 were determined to be eligible to participate in the study. Of the eligible Veterans, 342 took part in the in-person visit 1 (Interview Visit) which involved structured diagnostic interviews, neuropsychological testing, and self-report symptom questionnaires lasting approximately six hours and conducted by study personnel, such as staff (neuro)psychologists, study coordinators, and postdoctoral fellows. All study personnel completed a training process that included education, mock interviews, observing real interviews, and being observed during real interviews prior to data collection.

Participants who passed validity indicators during the Interview Visit were invited for a follow-up visit (Neuroimaging Visit) to obtain neuroimaging data, lasting approximately four

hours (see Appendix A for more detail on data availability limitations and steps taken to accommodate). Of the 232 participants determined to be eligible for the Imaging Visit, 201 ultimately completed that visit.

3.3 MEASURES

Performance and Symptom Validity. Participant data were excluded from analyses if any of the following conditions were met: Scoring higher than 23 on the Structured Inventory of Malingered Symptomatology (SIMS; G. P. Smith & Burger, 1997), scoring below the test manual's cutoff on any of the indicators (Immediate Recall, Delayed Recall, or Consistency) on the Medical Symptom Validity Test (MSVT; Green, 2004), or scoring above 120 on the b Test (>120, Boone et al., 2000). These same criteria were used in a recent similar study (Ord et al., 2023) to set thresholds for valid performance in a Veteran sample.

Combat exposure. The DRRI-2-D (Deployment Risk and Resilience Inventory, Version 2, Combat Experiences; Vogt et al., 2012) is a 17-item self-report questionnaire that captures combat-related circumstances such as firing a weapon, being fired on, being attacked or witnessing an attack (e.g., encountering an explosive device), and going on special missions and patrols that involve such experiences. The original scale (DRRI; King et al., 2003) was first developed in response to a lack of measures that capture the experiences of present-day combat deployments (Vogt et al., 2012). Items on the DRRI-2-D are rated on a 6-point Likert-like scale (1 = "Never" to 6 = "Daily or almost daily"). Total scores range from 17 to 102, with higher scores indicating greater exposure to combat. According to the test manual, experiences are considered objective events and circumstances that do not include subjective/personal interpretations of events (Vogt et al., 2012). Internal consistency was excellent in a sample of OEF/OIF Veterans ($\alpha = .91$), and the DRRI-2-D correlated significantly with a PTSD symptom

severity measure (r = .45; Vogt et al., 2012). The DRRI was also significantly associated with PTSD diagnostic status (Kearns et al., 2016).

Executive functioning components. The selection of candidate measures was guided by the theoretical frameworks informing our multidimensional conceptualization of EF (Diamond, 2013; Miyake et al., 2000). Accordingly, the following tests were considered as candidate measures: Trail Making Test B, Controlled Oral Word Association Test, Animal Naming, WAIS-IV (Matrix Reasoning, Similarities, Digit Span, Letter-Number Sequencing, Visual Puzzles, and Arithmetic).

Candidate measures. The Trail Making Test B (TMT-B; Bowie & Harvey, 2006) is a timed test involving alphanumeric sequencing and is commonly referred to as a test of set shifting and maintenance. Based on the available literature, the TMT-B is one of the most widely used measures of EF (Scott et al., 2015). Accordingly, we would expect the TMT-B to group with other measures of cognitive flexibility/inhibition under a shared factor. As higher raw scores indicate worse performance on this test, scores were inverted such that higher scores reflected better performance.

The Controlled Oral Word Association Test (Benton et al., 1983) is a verbal fluency task that involves phonemic word generation within a brief period (1 minute) for a specified letter from a sequence of letters, including F, A, and S. Animal Naming (contained in the Boston Diagnostic Aphasia Examination; Goodglass & Kaplan, 1983), another verbal fluency task, involves semantic word generation for the category "Animals", also within a 1-minute period. The COWAT phonemic (commonly referred to as FAS) and semantic fluency (Animal Naming, commonly referred to as Animals) tasks have been associated with a composite of fluid reasoning tasks (rs = .25 and .43, respectively), as well as a composite containing shifting tasks

(*r*s = .23 and .44, respectively; Aita et al., 2019), though as the authors commented, semantic fluency evidenced stronger relationships with both EF components. In addition, Johnco et al. (2015) observed a significant and positive relationship between the FAS and TMT-B. Thus, we expect FAS and Animals to load on a shared factor with other measures of cognitive flexibility/inhibition.

Six tests of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV; Wechsler, 2008) were included: Digit Span (DS), Letter Number Sequencing (LNS), Matrix Reasoning (MR), Visual Puzzles (VP), Arithmetic (AR), and Similarities (SIM).

The DS, AR, and LNS subtests are all components of the Working Memory Index (Wechsler, 2008). DS is composed of three parts: Digits Forward, Digits Backward, and Digits Sequencing. Digits Forward is primarily thought to be a measure of simple attention, whereas Digits Backward and Sequencing are thought to additionally reflect working memory capacity. In a multiple comparison examination of various factor models using the WAIS-IV/WMS-IV battery standardization sample, DS loaded consistently onto the Working Memory factor (Holdnack et al., 2011). LNS involves the presentation of a random series of numbers and letters. Respondents are then asked to repeat back the numbers in order first followed by the letters in alphabetical order. Prior factor-analytic work demonstrated that LNS, along with DS, accounts for a substantial amount of variance in working memory (Hill et al., 2010). In the same sample as noted above (Holdnack et al., 2011), AR loaded onto the Working Memory factor but also shared small cross-loadings with a Verbal Comprehension factor. Thus, while it may share loading with other factors, part of the variability in AR is attributable to Working Memory, consistent with its conceptualization in current clinical practice. Taken together, we expect that the DS, AR, and LNS subtests will load onto a Working Memory factor.

The SIM and MR subtests are thought to reflect verbal and nonverbal abstraction/reasoning, respectively. In a sample of older adults, another version of SIM (from the Wechsler Abbreviated Scale of Intelligence; WASI-II) was predictive of scores on a measure of instrumental activities of daily living (Nguyen et al., 2020), though the correspondent version of MR was not a significant predictor. A former version of MR (WAIS-III) evidenced shared variability with set-shifting tasks (Wisconsin Card Sorting Test, Stroop Color-Word Test) as well as other measures in the WAIS-III categorized under the Perceptual Organization Index (e.g., Block Design; Aken et al., 2014). VP, which measures abstraction and reasoning, concept formation, visuospatial organization, and attention/working memory, has previously correlated with tests of mental flexibility in a Veteran sample (Fallows et al., 2011). Thus, we expected that SIM, MR, and VP would share variability with other tests reflecting an underlying Cognitive Flexibility/Inhibition factor. The hypothesized factor structure is depicted in Figure 2.

ACC volume. Magnetic resonance imaging data were acquired on a 3 Tesla Siemens Skyra magnetic resonance imaging scanner using a high-resolution 32-channel human head/neck coil (Siemens Medical, Malvern, Pennsylvania) in accordance with the National Institute of Neurological Disorders and Stroke Common Data Elements advanced protocol recommendations including structural T1-weighted, T2-weighted, and FLAIR pulse sequences. FreeSurfer 6.0 was used for volume analytics (Fischl et al., 2002, 2004). Briefly, FreeSurfer automates the processing of three-dimensional neuroimaging data obtained from the imaging scanner, stripping the skull from the image, reconstructing the surface and volume, labeling/parceling anatomical areas, and condensing this large amount of data to reflect morphometric properties such as cortical thickness, gray matter width, and regional volumes. To obtain regional volumes, raw imaging data are matched against an atlas based on a large training dataset (MNI305) and

iteratively segmented based on probability, with an accuracy rate that is comparable to manual labeling (*FreeSurfer*, n.d.).

In terms of its anatomy, the ACC is located adjacent to and above the corpus callosum. Some basic neuroscience work divides this region into a dorsal posterior section, called caudal or dorsal ACC (dACC), and a ventral anterior section referred to as ventral or rostral ACC (rACC), with some anatomical studies proposing further subdivisions (Stevens et al., 2011). Given its role in the initial threat evaluation as well as the subsequent response (emotional, cognitive, physiological; Etkin et al., 2011), the dACC is thought to play a crucial role in the detection of conflicting information in the environment (Maier & di Pellegrino, 2012). The rACC is involved in the downregulation of the amygdala (sympathetic) response, supporting the extinction of fear responses when the feared stimulus is no longer present (Etkin et al., 2011). As it relates to the present work, appraisal processes and affect modulation are thought to be closely linked and central aspects of adaptation, thus we consider both dACC and rACC under the broader umbrella of ACC. Similarly, though some structural and functional neuroscience studies have attempted to distinguish the contributions of the two sides of the ACC (left versus right), either as a whole or when further divided into dACC and rACC, lateralization and regional division of the ACC has been inconsistent across studies. Given the novelty of the questions examined in this work, we consider the full, bilateral ACC as the region of interest in order to maximize our ability to test the role of the ACC in the relationship between combat exposure and current PTSD.

Bilateral rostral and dorsal ACC volume were summed. The regional total volume was then divided by intracranial volume, consistent with prior work in this area (e.g., Martindale et al., 2020). For ease of interpretation, a linear transformation was conducted by multiplying the ratio by an integer (10000).

PTSD continuous symptom severity and diagnosis. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, Weathers et al., 2018) is a 30-item questionnaire that corresponds to the DSM-5 diagnosis for PTSD. It is considered the "gold standard" in PTSD assessment. As a basis of symptom inquiry, questions posed are in reference to an "index" trauma identified at the outset of the interview. The measure provides two scoring algorithms: a CAPS-5 symptom severity score (continuous) based on symptom frequency and intensity with possible scores ranging from 0 to 80. Alternatively, individual symptom severity ratings of 2 or higher (i.e., the SEV2 rule) are indicative of symptom presence and are counted toward a PTSD diagnosis (yes/no). For the present study, we defined PTSD as the presence of a *current* PTSD diagnosis. While PTSD lifetime diagnostic data was available, this category also included any PTSD diagnoses that occurred prior to military service and we were interested in capturing predictors of variability associated with current PTSD. Additionally, as symptom severity reflects current PTSD symptomatology, using current PTSD diagnosis (rather than lifetime diagnosis) was the most appropriate to keep both variables on the same time scale. Internal consistency for the CAPS-5 full-scale was good in U.S. military Veteran samples ($\alpha = .88$; Weathers et al., 2018). Additionally, in support of the measure's convergent validity, the measure correlated with the PCL-5 ($r = .66$), the PHQ-GAD ($r = .47$), and the IPF (a measure of functional impairment across life domains; $r = .46$). Similarly, weaker associations ($r = .02$) with a measure of personality pathology (Psychopathic Personality Inventory; PPI) supported the measure's discriminant validity.

Demographic information. Participants were asked to provide information regarding their age, sex, educational history, history of combat deployments, and time since index trauma (i.e., the trauma of reference when evaluating for PTSD).

3.4 PLAN OF ANALYSIS

Data analyses and all visualizations were conducted in *RStudio*, using *R* v4.0.2 (R Core Team, 2020; RStudio Team, 2021). Complete case analysis was used to restrict the sample to cases without missing data, on a listwise basis, for each regression analysis separately. Prior to conducting the main analyses, normality assumptions were evaluated by visual examination of histograms and scatter plots. However, regressions are generally robust to minor deviations from normality (Schmidt & Finan, 2018), and residual plots were examined following analysis with results briefly summarized below each analysis.

Aim 1 analysis.

Exploratory Factor Analyses. Exploratory factor analyses were conducted with candidate measures selected based on the theoretical framework proposed by Miyake et al. (2000). Scree plots and eigenvalues were examined for evidence of a unidimensional factor or multiple factors, and subsequent principal axis factoring was followed by oblique (Promax) rotation. As there is limited if any guidance at this point regarding the evaluation of fit statistics as applied to exploratory factor analysis solutions, support for factor solutions was evaluated based on communalities, percent variance explained, and fit with the underlying theoretical model, striking a balance of both parsimony and explanatory value. Retention of tests to the final measurement model was determined by the strength of each item's loading, such that any items with a loading <.3 were not retained. Factor loadings from the final measurement model were then used as "weights" for individual test scores, such that the resulting composites (one for each supported latent factor) were calculated as the sum of its constituent standardized, weighted test scores (based on the approach by Snyder et al., 2015 and Johnco et al., 2015). These weighted test scores represented EF components in all subsequent analyses. While it remains important to

systemically test the factor structure of the different components of EF as addressed in greater detail above, we hypothesized that the shared variability between measures categorized under Cognitive Flexibility and Inhibition would be suggestive of a common underlying latent factor. We also expected shared variability in Working Memory test scores, which we hypothesized to group as a separate latent factor, though these two likely covary to a moderate degree. Following factor analysis, empirical factor solutions were interpreted in the context of theoretical and conceptual frameworks described above: factor loadings and loading patterns were considered to determine how best to label the underlying factors.

Aim 2 analysis. Hypotheses 2a and 2b (in which EF components served as moderators) were tested with multiple linear regression (Hypothesis 2a) and logistic regression (Hypothesis 2b). Variables were entered into the regression simultaneously, including all covariates, main effects, and product terms representing the interaction of combat exposure and each of the EF components. Hypotheses 3a and 3b (in which ACC volume served as the moderator) were tested with multiple linear regression (Hypothesis 3a) and logistic regression (Hypothesis 3b), in a manner to that described above for Hypotheses 2a and 2b.

Bootstrapped percentile confidence intervals (95% confidence intervals calculated from the 2.5 and 97.5 percentile ranks within the bootstrap sampling distribution) with 10,000 draws attempted were constructed for all relevant parameter estimates using the *boot* function. Models were evaluated based on the percentage of variance explained in the outcome variable for linear regressions (Model adjusted R^2) and by the area under the curve indicating the predictive strength of the model for logistic regressions (Model AUC percentage). Individual parameter estimates were examined for statistical significance and their confidence intervals for overlap with zero.

Covariates. Age, sex, and years of education were included as covariates in any regression analyses involving neuropsychological test scores given the use of raw scores (i.e., not demographically-adjusted). Other potential covariates, including time since trauma, current diagnosis of Major Depressive Disorder (MDD) based on the Structured Clinical Interview for DSM-5, and presence of deployment mTBI history, were considered for further evaluation on the basis of prior empirical findings and theoretical reasoning.

Though research has demonstrated mixed findings regarding the relationship between time since trauma and PTSD, findings from recent work noted that PTSD symptoms tend to improve as temporal distance from trauma exposure increases (Lee et al., 2020). Thus, contributions from time since trauma may be important to isolate by considering it as a potential covariate. Additionally, it is not uncommon for individuals diagnosed with PTSD to have a comorbid diagnosis of MDD. Specifically, meta-analytic work provides prevalence rates of about 52% in mixed adult samples (Rytwinski et al., 2013), with even higher estimates in combat-exposed Veteran samples (Goetter et al., 2020). Importantly, while PTSD and MDD are thought to share overlapping symptoms of negative affect, Post et al. (2011) also highlights the need to examine them as separate constructs. As such, this warrants the consideration of current MDD diagnosis as a covariate in order to examine unique effects on PTSD (when accounting for MDD status). Deployment TBI has previously been identified as a risk factor for the development of PTSD (Loignon et al., 2020) and shown to increase in prevalence at higher levels of combat exposure severity (Troyanskaya et al., 2015). Variables were ultimately included as covariates if they were related to any of the predictor variables (combat exposure, Cognitive Flexibility, Working Memory, ACC volume) or outcome variables (PTSD symptom severity score as well as diagnostic status).

CHAPTER 4: RESULTS

Of the eligible participants who completed the Interview Visit, the performance of 98 participants was considered invalid (28.9%). Data from these participants were excluded from the analyses, resulting in a total analytical sample of 241 participants. This proportion of subthreshold performance on validity indicators is consistent with prior research with Veteran populations (Etzel et al., 2024). T-test and chi square analyses revealed statistically significant group differences between participants whose performance fell above versus below validity thresholds on several variables (see Table 1). Specifically, participants whose performance was considered "invalid," had a higher average percent service-connection, presence of current MDD diagnosis, proportion of deployment mTBI, self-reported combat exposure severity, PTSD symptom severity rating per CAPS-5, proportion of PTSD diagnoses per CAPS-5, co-occurring MDD and PTSD, and performed worse on several neuropsychological tests, including SIM, DS, VP, AR, LNS, TMT-B, and Animals. There were no significant group-level differences for age, sex, education, branch of service, service-connection status (yes/no), lifetime mTBI, time since trauma, and performance on MR and FAS. Table 1 outlines the demographic characteristics of the analytical sample and group-level differences noted above. Overall, mean performance across all nine tests using demographically-adjusted T scores was considered average based on the American Academy of Clinical Neuropsychology consensus labels (Guilmette et al., 2020).

4.1 AIM 1: FACTOR ANALYSIS

Skewness and kurtosis values for variables of interest were within acceptable limits. Prior to conducting the factor analysis, Mahalanobis distances were calculated and significance testing informed removal of multivariate outliers ($N = 7$). This resulted in a total of 234 participants. As an initial step in the factor analysis, bivariate correlations among all nine neuropsychological

tests were examined, which revealed significant relationships among all variables (*r*s = .21 - .61, *p*s < .01; see Table 2). In some cases, correlational matrices may provide guidance about groups of variables with shared variance, as indicated by higher intercorrelations in one "area" of the matrix. However, examination of the correlation matrix for the variables included in this factor analysis did not indicate any groups of especially highly correlated variables.

Although a scree plot suggested the presence of one factor, subsequent parallel analysis revealed the possible presence of up to three factors; thus, 1-, 2- and 3-factor solutions were tested in accordance with our analytic plan. Overall, the 1-factor solution accounted for 38% of the variance among all included tests with loadings ranging from .51 to .68. The 2- and 3-factor solutions resulted in Heywood cases, which refers to the presence of impossible parameter values over 1, suggesting that a factor accounts for 100% or more of a variables' variance. Heywood cases can occur for a number of reasons, including but not limited to overextraction of factors, small sample size (which may provide unstable estimates), or overly large or small factor loadings (Cooperman & Waller, 2022). Heywood cases render the factor solution invalid as implausible values in the factor analyses can bias model interpretations. Re-examination of the solutions indicated that FAS produced an implausible parameter value in both solutions. In addition, FAS and Animals consistently demonstrated the highest loadings with the same overarching factor, which had weak loadings with other tests (e.g., MR, VP) and was therefore determined to unlikely be a component of EF per our conceptualization. Specifically, the strong emphasis on language skills for both FAS and Animals may have been the reason for their shared variability (rather than EF), thus we removed these variables from our factor analysis. This will be described further in the Discussion section.

After removing FAS and Animals to focus on the EF components of interest, a revised scree plot suggested the presence of 1- or 2- factor solutions. The 1-factor solution accounted for 41% of the variance with loadings ranging from .47 to .70, and the 2-factor solution accounted for 50% of the variance with loadings ranging from .37 to .90 (factor 1) and .65 to .98 (factor 2). Though both solutions were equally empirically plausible, the 2-factor solution was more theoretically consistent as we intended to capture both the "unity" and "diversity" of EF, as previously discussed. Thus, the 2-factor model was retained (see Table 3), with one factor termed "Cognitive Flexibility" (CF) and the other factor termed "Working Memory" (WM) as components of EF (Miyake et al., 2000). Although the first factor was initially hypothesized to represent "Cognitive Flexibility/Inhibition," the inhibition aspect of the factor was not interpreted to be present in the final solution due to lack of availability of included neuropsychological tests (see Appendix A) resulting in few if any included tests specifically measuring inhibition skills. As a result, the factor we identified more likely represented cognitive flexibility rather than inhibition or a combination of the two.

Regression-based weighting was used to estimate scores for the CF and WM factors based on all available factor loadings from the 2-factor solution. This resulted in each participant receiving a "Cognitive Flexibility" score and a "Working Memory" score. These resulting factor scores were used as independent variables in subsequent analyses (Aim 2). For ease of interpretation given the metrics of the other variables, raw factor scores were linearly transformed by multiplying all values by 10.

4.2 AIM 2: EXECUTIVE FUNCTIONING COMPONENTS AS MODERATORS

Of the 234 participants, a total of eight participants were excluded from Aim 2 analyses as their score on the combat exposure severity scale (subsequently referred to as "combat

exposure") was outside of the plausible score range (score of 16 on a scale with a valid range between 17-102). Though the cause of this is unknown (as can be the case with secondary data usage), it is most likely attributable to data entry errors. As done previously, Mahalanobis distances were calculated for DRRI-2 and CAPS-5 and significance testing informed removal of likely multivariate outliers (N = 32), resulting in a total of 194 participants.

Bivariate correlations between variables of interest for EF component models (i.e., combat exposure, CF, WM, PTSD symptom severity, PTSD diagnostic status) reflected strong associations between CF and WM (r = .8) and between combat exposure and PTSD symptoms (r = .22) and diagnosis (r = .18), and the absence of support for relationships between EF components and combat exposure or PTSD symptoms/diagnosis. Correlations are reported in full in Table 4. To inform the inclusion of covariates in EF component regression analyses, correlations between the variables of interest and demographic variables were conducted. Based on these correlations, age, sex, years of education, time since trauma, current MDD diagnosis, and deployment TBI were included as covariates in subsequent analyses. A detailed description of bivariate correlations tested to inform covariate inclusion can be found in Appendix B.

Executive Functioning Components as Potential Moderators between Combat-PTSD Symptom Severity

A multiple regression analysis was conducted to examine the association of PTSD symptom severity with combat exposure, CF, WM, and/or the interaction between CF and combat exposure, and WM and combat exposure (see Table 5). Of the 194 participants, five were removed due to missingness (listwise deletion). The model was statistically significant $F(11, 177) = 4.52$, $p = < .001$, adjusted $R^2 = .1707$), indicating that the full model explained approximately 17% of the variability in PTSD symptom severity. Of the covariates, sex (b =

6.83, $p = .018$) and current MDD diagnosis ($b = 15.33$, $p < .001$) emerged as significant predictors of PTSD symptom severity when all other variables in the model were held constant. Combat exposure emerged as a significant predictor ($b = 0.22$, $p = .007$), but neither CF or WM, nor their interactions with combat exposure (CF x combat exposure; WM x combat exposure) were significantly associated with PTSD symptom severity. With interaction terms excluded from the model, variance inflation factor values were within acceptable limits (all VIF < 5), suggesting low likelihood of model bias due to multicollinearity. Visual examination of plotted model residuals did not suggest any concerning pattern suggestive of heteroscedasticity.

Executive Functioning Components as Potential Moderators between Combat-PTSD Diagnostic Status

A logistic regression analysis was conducted to assess whether combat exposure, CF, WM, and/or the interaction between CF and combat exposure, and WM and combat exposure were associated with a change in the odds of an individual receiving a PTSD diagnosis based on the CAPS-5 (see Table 6). Only sex ($OR = 2.87$, $p = .039$) and current MDD diagnosis ($OR = 5.15$, $p = .002$) were associated with greater odds of a PTSD diagnosis. Though not associated with a practically meaningful change in odds, combat exposure was associated with a statistically significant change in odds of a PTSD diagnosis ($OR = 1.04$, $p = .027$). Neither CF or WM, nor their interaction with combat exposure were associated with a change in odds of PTSD diagnosis. In addition to the above analyses, a receiver operating characteristic (ROC) curve was plotted to examine the sensitivity and specificity of predictions for this logistic regression model and yielded an area under the curve (AUC) value of .72. This means that the model is 72% accurate in correctly predicting diagnostic status in our sample, which suggests mild improvement on random classification (i.e., AUC = .50).

4.3 AIM 2: ACC VOLUME AS A MODERATOR

Multivariate outlier identification using Mahalanobis distances resulted in exclusion of 32 cases. Bivariate correlations between variables of interest for ACC models (combat exposure, ACC volume, PTSD symptom severity, PTSD diagnostic status) reflected associations between combat exposure and PTSD symptoms (r = .23) and diagnosis (r = .20), and the absence of support for relationships between ACC volume and combat exposure or PTSD symptoms/diagnosis. Correlations are reported in full in Table 7. As above, to inform the inclusion of covariates in ACC models, correlations between the variables of interest and demographic variables were conducted. Sex, years of education, and time since trauma did not correlate with any of the variables of interest. Thus, only age, current MDD diagnosis, and presence of deployment TBI were included as covariates in subsequent analyses. A detailed description of bivariate correlations evaluated for covariate inclusion in models can be found in Appendix B.

ACC Volume as a Potential Moderator between Combat-PTSD Symptom Severity

A multiple regression analysis was conducted to examine the association of PTSD symptom severity with combat exposure, ACC volume, and the interaction between combat exposure and ACC volume (see Table 8). The model was statistically significant $F(6, 130) = 4.53$, $p < .001$, adjusted $R^2 = 0.1348$), indicating that the model explained approximately 13% of the variability in PTSD symptom severity. Only current MDD diagnosis ($b = 6.64$, $p < .001$) emerged as a significant predictor of PTSD symptom severity. Combat exposure, ACC volume, and their interaction were not significant ($p > .05$). With interaction terms excluded from the model, variance inflation factor values were within acceptable limits (all VIF < 5), suggesting

low likelihood of model bias due to multicollinearity. Plotted model residuals did not demonstrate any concerning pattern suggestive of heteroscedasticity upon visual examination.

ACC Volume as a Potential Moderator between Combat-PTSD Diagnostic Status

A logistic regression analysis was conducted to assess whether combat exposure severity, ACC volume, and/or their interaction predicted the odds of an individual receiving a PTSD diagnosis based on the CAPS-5 (see Table 9). Similar to the linear regression model results, current MDD diagnosis (OR = 1.87, p = .03) was associated with an increase in the odds of a PTSD diagnosis. Combat exposure, ACC volume, and their interaction were not significant (p >.05). In addition to the above analyses, a receiver operating characteristic (ROC) curve plotted to examine the sensitivity and specificity of the logistic regression model predictions yielded an area under the curve (AUC) value of .68. This means that the model is 68% accurate in correctly predicting diagnostic status in our sample, which suggests only a small amount of improvement on random classification (i.e., AUC = .50).

CHAPTER 5: DISCUSSION

The objectives of this study were to identify the best-fitting factor structure for EF (informed by the work of Miyake et al., 2000) and to examine the extent to which EF components and ACC volume interact with past combat exposure to predict current PTSD symptom severity or PTSD diagnostic status. While we were able to replicate the proposed two-factor structure (Aim 1), representation of the factors was limited due to the available tests. Regression analyses indicated that across all models, current MDD diagnosis was the most consistently predictive of PTSD symptoms and PTSD diagnostic status. However, our EF factors, CF and WM, and ACC volume did not moderate the relationship between combat exposure and PTSD symptom severity or diagnosis.

In partial support of hypothesis 1, a correlated 2-factor structure demonstrated adequate fit and was the most consistent with the model specified by Miyake et al. (2000). Though the 1-factor model also had adequate fit, its unidimensional structure was limited in that it failed to allow for the "diversity" aspect of Miyake et al.'s (2000) model of EF, which posits that EF is best conceptualized as consisting of separable (i.e., "diversity) and related (i.e., "unity") cognitive abilities. In the 2-factor model, unity was reflected in the correlation between factors, and diversity in the pattern of loadings. Yet, the factor analysis suggested that both factors had loadings of varying strengths for nearly all the tests included (i.e., cross-loadings). This pattern is consistent with what has been referred to as the "task impurity" problem (Snyder et al., 2015), as neuropsychological tests such as those used in the current work often require multiple cognitive skills (e.g., language, processing speed, executive functioning) for adequate performance. As such, they share variance with other tests measuring the same areas, yet have some unique variance specific to that test.

For example, the WAIS-IV AR subtest unexpectedly was more closely related to the CF factor in comparison to the WM factor. Originally, we hypothesized that AR would be most closely associated with WM consistent with current clinical neuropsychological guidance regarding this subtest, which is thought to primarily require basic mental manipulation skills. However, unique aspects of AR, such as the lack of continuity between individual items, may require CF-related skills such as set-shifting (re-focusing on the details and operations required for the next item's scenario) versus simply mentally rehearsing and manipulating information (working memory). Consistent with this conceptualization of AR as requiring more than working memory skills, a recent study demonstrated that AR was more strongly associated with math ability than either DS or LNS (Harrison et al., 2024). The researchers concluded that AR may be more complex and thus less "pure" than other tests conceptualized as measuring working memory. In addition, Harrison and colleagues (2024) found a higher correlation between DS and LNS than between either of these tests and AR, and these differential relationships were replicated in our work as well, supporting our inclusion of LNS and DS on the WM factor, and our exclusion of AR.

In contrast to our 2-factor model interpreted as "cognitive flexibility" and "working memory," Karr et al. (2018) summarized a variety of alternative EF model configurations, concluding that EF model configurations are context-dependent such that they may not necessarily exhibit the same factor structure in each setting, population, or set of tests. Yet, many of these configurations, consistent with the unity-diversity model (Miyake et al., 2000), included an inhibition factor, which we did not identify in our factor analysis. Differences in neuropsychological tests available and in sample characteristics (see Appendix A) may help explain why our model may have been inconsistent with the structures proposed by Karr and

colleagues. Specifically, tests such as those based on the Go/No-Go paradigm (Gomez et al., 2007), the Stroop Color and Word Test (Golden & Freshwater, 2002), and the NIH Toolbox Flanker Inhibitory Control and Attention Test (Weintraub et al., 2014) are some examples that are widely used in research and clinical practice to capture prepotent response inhibition ability, or the ability to suppress a response that is no longer relevant (e.g., DeGutis et al., 2015; Mungas et al., 2014; Swick et al., 2011, 2012). Future studies should plan to collect data on a wider variety of neuropsychological tests to ensure adequate domain coverage.

Interestingly, FAS and Animals, which were included in the initial factor analysis, clustered together outside of the hypothesized model and shared little variance with the other tests. This suggests that something shared and specific to these tests, such as language skills, may have been the reason they clustered together. That is, while performance on FAS and Animals may also be influenced by EF, as is suggested by its clinical/practical uses and interpretations, the initial factor analysis in the present study yielded a separate factor loading on FAS and Animals, with low if any loadings on other tests, suggesting that the shared variance specifically between these two tests was unlikely to be related to EF as conceptualized in this study. Indeed, prior work has demonstrated that with the inclusion of other language-based tests, FAS and Animals loaded with a "language" factor (with Boston Naming Test and WAIS-IV Vocabulary) instead of the "executive functioning" factor (with WCST and TMT-B; Whiteside et al., 2016). Statistically, when examining the amount of variance explained by the different one-factor models, the model without FAS and Animals accounted for slightly more variance (.41) compared to the one that included these two tests (.38), suggesting that retaining these tests diminished the overall model fit.

With regard to hypothesis 2, we did not find support for either of the EF components in our study, WM and CF, as moderators of the relationship between combat exposure and PTSD. This may be unsurprising given that we also did not observe direct associations between WM or CF and PTSD (symptoms or diagnostic status). Our findings are inconsistent with prior meta-analytic work documenting support between EF and PTSD symptoms across multiple studies (Polak et al., 2012; Scott et al., 2015). Yet, differences in the tests used and in the composition of the specific EF components may have also contributed to differences between our findings and those in the literature. Broadly, our findings contrast with what has been previously suggested by Aupperle et al. (2012), who described EF deficits as risk factors associated with PTSD development.

One possible explanation could be inadequate sampling of the EF construct(s) across our WM and CF subfactors, such that the components or skills associated with PTSD were not captured by the tests we used or the factors we identified. As a specific example, the tests we included likely did not possess enough shared variance related to inhibition, resulting in no inhibition factor being identified among the tests and inadequate coverage of the inhibition skill in our representation of EF in this work. More globally, our range of overall EF may have been somewhat restricted, as the neuropsychological test performance of individuals in our sample generally fell in the average range. Consequently, it is possible that an effect is present in individuals with impaired EF, that is, EF skills at the lower end of the distribution (e.g., those with moderate-to-severe TBI). Future research could test this possibility by utilizing purposive sampling to recruit individuals with EF skill at all levels along the distribution.

Though conceptually inconsistent with the cognitive model of PTSD, EF may simply not moderate the relationship between combat exposure and PTSD. Recent work did not find support

for an EF composite as a moderator (Etzel et al., 2024; Liu et al., 2023) and our null findings suggest that individual EF components also do not moderate the combat exposure-PTSD relationship. Thus, researchers may consider examining interaction effects between combat exposure and other potentially relevant domains of cognitive functioning. Given the centrality of traumatic memories, learning and memory may be another relevant area of focus for continuing to investigate the role of cognitive functioning in the development and persistence of PTSD symptoms (Brewin, 2011).

Alternatively, it may be that our operationalization of PTSD symptoms as a global severity score obscured differential relationships between EF components and PTSD symptom clusters, as has been found in prior work using an EF composite (Wrocklage et al., 2016). Unfortunately, the present study was underpowered for examining specific PTSD symptom cluster-level relationships and interactions. Future work could focus on the re-experiencing symptom cluster, as symptoms such as flashbacks may be more closely associated with some EF components from Miyake et al.'s framework (2000) such as cognitive flexibility and/or inhibition difficulties given their role in shifting away from irrelevant information, and less closely associated with working memory.

Our finding of a significant association between combat exposure and both PTSD symptom severity and PTSD diagnosis in our EF models aligns with prior literature documenting a relationship between combat exposure and PTSD (e.g., Ramchand et al., 2010; 2015). Yet, the lack of consistency in the association between combat exposure and PTSD across all of our models may be the different numbers/types of covariates. As noted above in relation to EF, the absence of evidence for an effect in our work may also be due to PTSD symptom cluster-level relationships which were obscured by using the global score as an outcome. Indeed, Miller

(2008) has demonstrated significant relationships between combat exposure and re-experiencing (measured using the CAPS). Considering our work in the context of extant literature, even remote past combat exposure remains an important longitudinal risk factor for PTSD. Thus, VHA and other settings providing post-deployment care for Veterans may consider implementing or continuing periodic screening of individuals exposed to combat for persistent or new-onset PTSD symptoms to facilitate early detection and intervention, in line with efforts to promote positive post-deployment mental health (Brancu et al., 2017).

In the present study, current MDD diagnosis emerged as a significant predictor of current PTSD symptoms and diagnosis. Researchers have commented on the importance of examining MDD and PTSD as separate constructs (Post et al., 2011), supporting our approach of accounting for current MDD when examining the unique relationship between combat exposure and PTSD. However, though each diagnosis has unique features, prior work also recognizes symptom overlap between PTSD and MDD, including transdiagnostic general "distress" or more specifically, the negative alterations in mood and cognitions that are often present in both conditions (Barlow et al., 2010; Post et al., 2011). Similarly, researchers have begun to examine underlying neural processes that may be shared by both conditions to advance our understanding of etiology and recommendations for intervention (Polski & Vaidya, 2021). From a measurement perspective, it is important to note that both MDD and PTSD were assessed via clinician-administered interviews, meaning that some of their relationship may represent common method variance. To manage the influence of common method variance, future research intending to study PTSD in isolation may want to consider different forms of establishing presence of MDD symptoms and/or a diagnosis (e.g., self-report, chart review).

With regard to hypothesis 3, we did not find support for ACC volume as a moderator of the relationship between combat exposure and PTSD symptoms or odds of a PTSD diagnosis. While previous research has identified ACC as having a role in the threat response (Etkin et al., 2011; Giuliani et al., 2011), we did not observe any direct or interactive associations between the ACC volume and PTSD symptoms or odds of a PTSD diagnosis. Our null findings are difficult to contextualize within a small body of prior literature that has selectively examined different (and at times inconsistent) divisions within the ACC (e.g., Doherty et al., 2015). The amygdala, which is thought to be regulated in part by the ACC, has also accrued an inconsistent basis of support for volumetric differences between individuals with PTSD when compared with trauma-exposed and non-exposed individuals. Thus, static volumetric data may be insufficient to reflect the dynamicity of conflict detection (Botvinick et al., 2001, 2004) and emotion regulation proposed by the neurocircuitry model of PTSD (Rauch et al., 1998). Specifically, while smaller regional volume may suggest regional hypoactivation (Qing & Gong, 2016), the neurocircuitry model posits that, rather than PTSD symptoms being attributable to dysfunction in any single area, inadequate "top-down" regulation of the amygdala by the ACC and other areas within the vmPFC potentiate maladaptive threat responses (Rauch et al., 2006). Thus, functional neuroimaging may be critical to understanding the role of the ACC in the combat exposure-PTSD relationship as it would permit contextualization of the ACC within its threat regulation circuit (Rauch et al., 1998).

Additionally, a closer examination revealed that across our sample, ACC volume was not lower in those diagnosed with PTSD, which is inconsistent with several studies documenting differences in ACC volume between those with and without current PTSD diagnosis (Chao et al., 2013; Karl et al., 2006; Li et al., 2014; O'Doherty et al., 2015; Woodward et al., 2006). It is

possible that those who had the most severe PTSD may not have been captured in this sample, limiting our ability to detect PTSD diagnostic group-level or symptom severity differences in ACC volume. Yet, even in our sample with an average of 13 years since trauma exposure and EF largely in the average range, bilateral ACC volume in our sample (M = 9057 mm^3; no group level differences between those with and without a PTSD diagnosis) was similar to previously documented bilateral ACC volumes in combat-exposed Veterans with (M = 9672.47 mm^3) and without (M = 9711.72 mm^3) a PTSD diagnosis (not statistically significantly different; Young et al, 2018). These volumes are in contrast to those previously reported for right-handed healthy female volunteers (M = 12807 mm^3; Giuliani et al., 2011), though like ours, Veteran samples typically consist of fewer female individuals and prior work suggests that women have relatively larger gray matter volume in the cingulate cortex (Mann et al., 2011). Of note, many studies did not report raw ACC volumes, limiting our ability to make even surface-level comparisons between non-trauma exposed individuals and those with trauma exposure. However, at least this observation of higher ACC volumes in non-trauma exposed individuals (though restricted to female individuals) is one indication that restricting our sample to combat-exposed Veterans may also have restricted the range of ACC volumes, constraining variability and limiting the possibility of identifying associations.

Though we tested separate models for diagnostic status and symptom severity, models were generally consistent in that interaction terms were non-significant and non-contributory across all models, and no models identified associations between EF components or ACC volume and PTSD symptoms *or* diagnosis.

5.1 STRENGTHS AND LIMITATIONS

Strengths of the present work included our development and use of empirically-derived factor scores to systematically reflect EF in a Veteran sample, based on a factor analysis that prioritized both the hypothesized unity and the diversity of EF. In addition, this study used a validated clinician-administered interview to measure PTSD symptoms and to determine diagnostic status. Indeed, much of the work in this line of research assesses PTSD using self-report measures such as the PTSD Checklist for DSM-5, which is thought to primarily capture general distress rather than PTSD symptomatology (Miskey & Shura, 2017), and may therefore be less stringent than the CAPS-5 when seeking to examine predictors of PTSD. Overall, our study contributed to the theoretical conceptualization of executive functioning in a combat Veteran sample, for whom the factor structure of executive functioning has been infrequently examined. Aspects of military culture and experiences, such as needing to quickly adjust and manage complex tasks in combat settings, may influence the relevance of different components of EF, underscoring the importance of systematic testing of EF factors. In addition, studies examined by Karr et al. (2018) had samples with average ages below 30 and over 50, whereas our sample had an average age of approximately 40, thus expanding the literature base to better cover the full range of middle-aged adults.

Yet, this work was not without its limitations, which are important to consider when interpreting the results. As noted previously, our factor analysis and combination of tests suggested that we were not able to fully represent the three sub-components included in Miyake et al.'s (2000) representation of EF, which was the basis for our initial hypotheses. In addition to the notable absence of tests capturing inhibition skills, our findings are a reflection of the specific neuropsychological tests used in the study. Additionally, we were not able to obtain any

information about the racial/ethnic identities of the study participants, which limits our ability to characterize our sample and generalize the results to the broader Veteran population.

Although our sample size is comparable to other studies examining similar questions, moderation effects, being based on a combination of main effects, tend to be smaller than main effects and therefore more difficult to detect. Thus, while our models were adequately powered for overall significance testing, they were underpowered to test for the significance of specific effects. In part, this may have been due to the necessity of removing participants based on data validation (i.e., plausibility checks, symptom and performance validity testing), which resulted in approximately 70% of our sample being retained to final analyses.

This secondary analysis was also shaped by the inclusion criteria of the primary study, which excluded individuals with a current substance use disorder, severe psychopathology, and individuals with moderate-to-severe TBI. Although these exclusion criteria are commonly applied in this area of research (e.g., Scott et al., 2015; Woon et al., 2017), they may have also resulted in range restriction on our PTSD measure given that individuals with both PTSD and SUD likely have more severe PTSD symptoms and may be more likely to be diagnosed with PTSD as a result. Across studies, researchers often use targeted sampling strategies to match individuals diagnosed with PTSD to controls, making comparison of prevalence rates for diagnoses challenging. On average, the prevalence rates of current PTSD (around 28%) in our sample of combat Veterans who passed symptom and performance validity indicators is comparable to the proportion observed in a sample of 3,247 US military Afghanistan/Iraq Veterans (Brancu et al., 2017; PTSD = 29%; MDD = 22%; comorbid MDD and PTSD = 15%), yet our sample had a much lower proportion of individuals diagnosed with current MDD (around 9%), or current comorbid MDD and PTSD (5%; categories not mutually exclusive). One

potential contributor to our low proportion of individuals with MDD and comorbid MDD and PTSD may have been that this study excluded individuals with current substance use disorder, potentially resulting in a sample with overall less severe symptomatology.

Additionally, the average time since trauma in our sample was about 13 years, which may not be representative of the typical Veteran seeking treatment for PTSD symptoms. Though there is substantial heterogeneity in time since trauma among combat-exposed Veteran study participants in published research, symptoms tend to improve over time (Lee et al., 2020), consistent with our sample experiencing relatively low PTSD symptom severity.

In sum, our findings may not generalize well to those who have experienced moderate-to-severe TBI, have active substance use disorders or more psychopathology in general, or whose PTSD symptoms are more acute and/or are so severe that they would be unable to complete the in-person study activities. Purposive oversampling of sub-populations of individuals exposed to combat with historically excluded experiences (e.g., active substance use disorder, moderate-to-severe TBI) may improve our awareness of how the relationships of interest present in these uniquely challenging contexts.

5.2 RESEARCH IMPLICATIONS AND FUTURE DIRECTIONS

Because our EF components of CF and WM were not associated with PTSD symptoms or diagnostic status, future studies might include a greater variety of tests thought to be associated with one or more EF components, including both experimental cognitive psychology tests (such as the *n*-back) as well as more common neuropsychological tests (such as the Trail Making Test) to allow for a more comprehensive examination of the factor structure and the interpretation of factors.

Finally, to more comprehensively test the unique contributions of EF and ACC volume to PTSD symptoms following combat exposure, researchers should consider the effect of treatments, such as psychiatric (psychotropic) medication or psychotherapy, that may have the potential to significantly alter the course of PTSD symptoms and/or the relationship between combat exposure and PTSD. Unfortunately, we did not have access to this type of information about our sample. Finally, as noted above, functional neuroimaging may be critical to understanding the role of the ACC within the threat regulation circuit (Rauch et al., 1998).

5.3 PRACTICAL IMPLICATIONS

Though these preliminary tests of EF and ACC volume as moderators in the relationship between combat exposure and PTSD did not yield support for our hypotheses, our replication of the association between MDD and PTSD underscores the need to comprehensively assess not only for PTSD but also for MDD. Similarly, consistent with prior work, combat exposure emerged as a risk factor for PTSD, underscoring the importance of periodic screening of PTSD symptoms in this population.

5.4 CONCLUSION

This study was a novel examination of EF and ACC volume as potential capacities supporting adaptation after transitioning back to the civilian context after deployment. In other words, we sought to understand the role of EF and ACC in the relationship between past combat exposure and current PTSD symptoms/diagnosis, with a focus on processes relevant to the long-term cognitive and emotional reintegration to civilian life following combat deployment. As such, it was an initial foray toward advancing theoretical, empirical, and clinical understandings of the factors contributing to persistent symptoms of PTSD in Veterans. Our study contributed to the theoretical conceptualization of executive functioning in a combat Veteran sample, for whom

the factor structure of executive functioning has been infrequently examined. Aspects of military culture and experiences, such as needing to quickly adjust and manage complex tasks in combat settings, may influence the relevance of different components of EF, underscoring the importance of systematic testing of EF factors in our sample. In addition, our examination of EF bridged cognitive neuroscientific theories, which focus on hierarchical models of EF with multiple components (e.g., Miyake et al., 2000), with clinical neuropsychological theories regarding the contribution of tests commonly used in practice. Further, our inclusion of ACC volume as a potential moderator contributed to a growing awareness of multiple brain regions which may be relevant to PTSD and adaptation. Though we did not identify any significant associations between PTSD diagnostic status/symptom severity and Cognitive Flexibility, Working Memory, or ACC volume, our initial tests have the potential to inform future work in larger samples with a greater range of severity in symptoms.

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FIGURES

Figure 1. Participant Flow Diagram

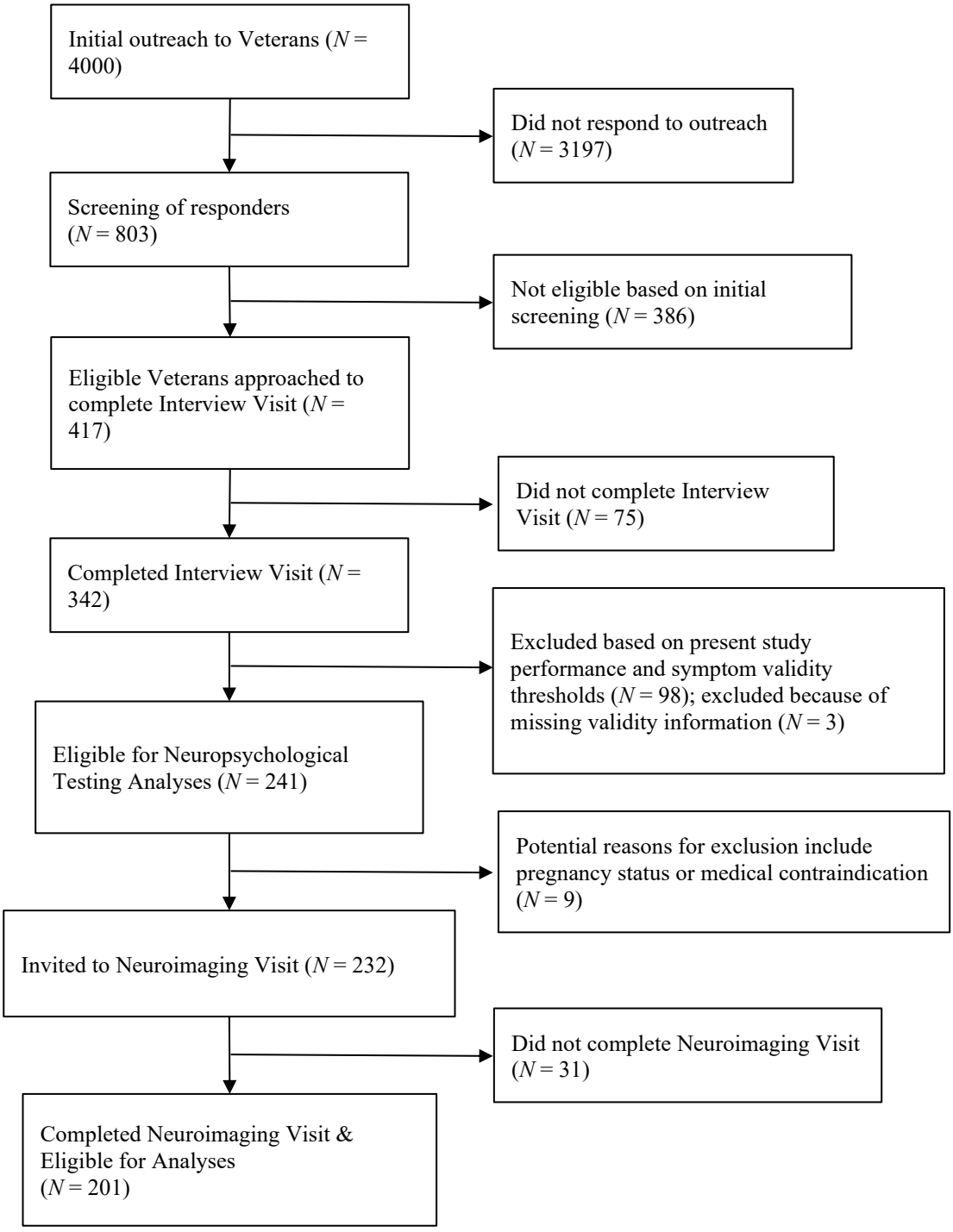
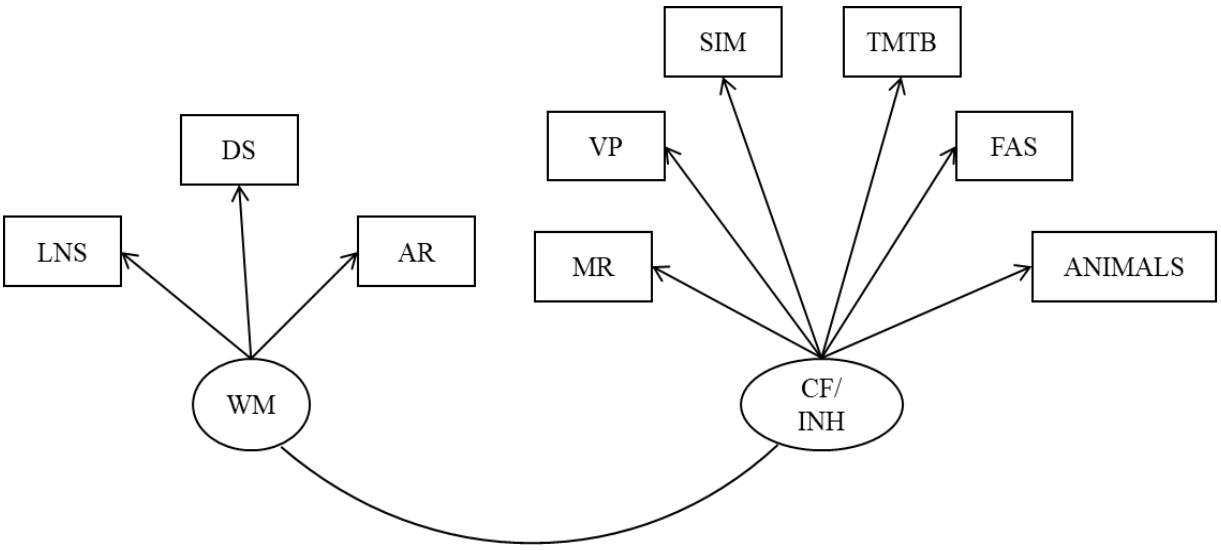
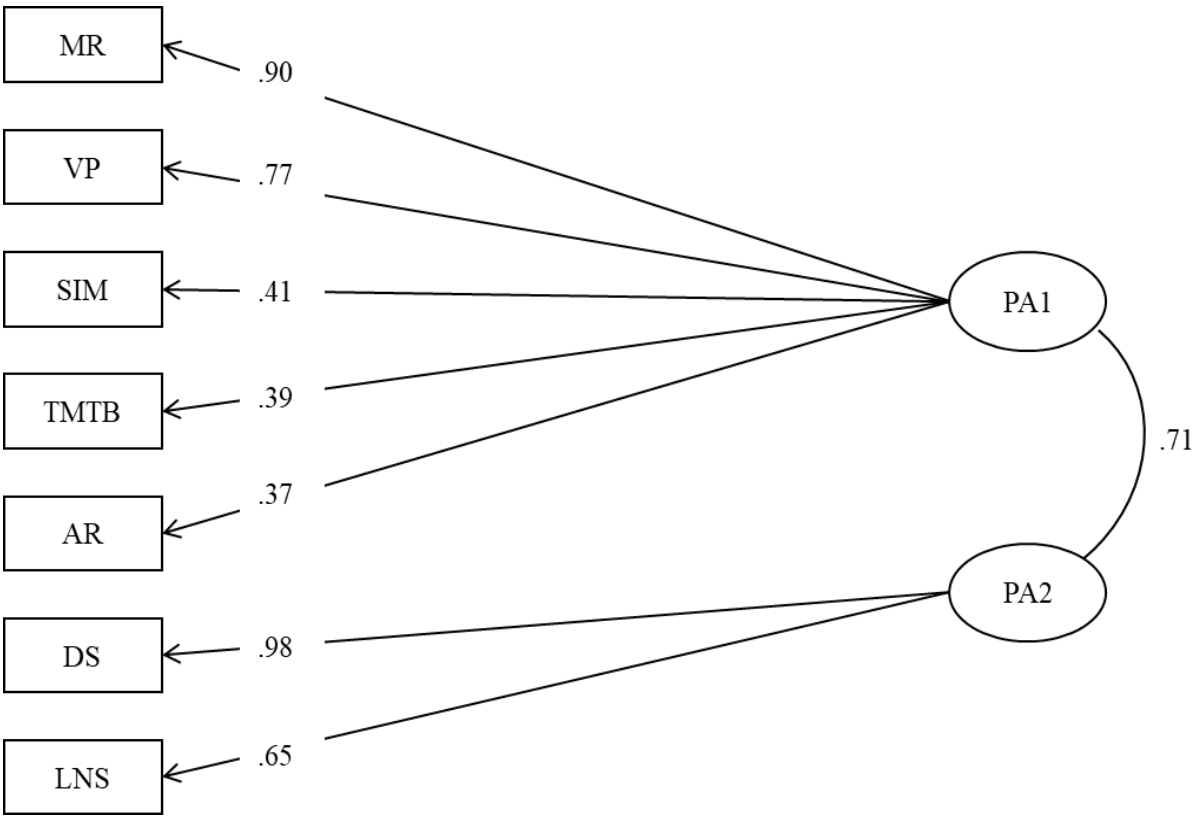


Figure 2. Hypothesized Factor Structure of Executive Functioning



Note. LNS = Letter Number Sequencing; DS = Digit Span; AR = Arithmetic; MR = Matrix Reasoning; VP = Visual Puzzles; SIM = Similarities; TMT B = Trail Making Test B; FAS = Controlled Oral Word Association Test-FAS Phonemic Fluency; Animals = Animal Naming; WM = Working Memory; CF = Cognitive Flexibility; INH = Inhibition

Figure 3. Retained Two-Factor Model of Executive Functioning



Note. Exploratory factor analysis yielded two factors, which were interpreted as "Cognitive Flexibility" (PA1) and "Working Memory" (PA2). MR = Matrix Reasoning; VP = Visual Puzzles; SIM = Similarities; TMT B = Trail Making Test B; AR = Arithmetic; DS = Digit Span; LNS = Letter Number Sequencing.

Table 1. Demographic Characteristics of Participants with Valid and Invalid Performance

	Valid ($N = 241$)				Invalid ($N = 98$)				t/χ^2	p
Variable	%	*M*	*SD*	Range	%	*M*	*SD*	Range		
Age (yrs)		41.68	10.2	23-71		41.32	9.57	26-65	.312	.756
Sex										
Male	86.00				86.73				1.489	>.999
Education (yrs)		15.11	2.15	9-22		14.66	2.14	12-21	1.747	.082
Branch of service[a]										
Army	72.20				72.45				.000	>.999
Marine Corps	11.20				10.20				.006	>.999
Air Force	9.54				10.20				<.001	>.999
Navy	7.05				7.14				<.001	>.999
Service-connected										
% rating		66.04	29.21	0-100		78.09	23.2	0-100	-3.774	.001
Status (yes)	95.15				98.88				1.483	.224
Current MDD diagnosis	8.71				25.51				15.358	<.001
Comorbid MDD/PTSD diagnosis	5.39				19.39				14.364	<.001
mTBI										
Deployment	44.81				63.27				8.765	.003
Lifetime	76.76				84.69				2.189	0.139
DRRI-2		34.19	14.04	17-93		43.66	19.55	17-91	-4.631	<.001
Combat Exposure[b]										
Time since trauma (yrs)		12.8	8.1			12.3	6.9	1.5-41.3	.455	.650
Neuro-										

psychological									
Test Results[c]									
WAIS-IV	49.49	10.12	24-90		44.93	10.67	21-71	3.624	<.001
SIM									
WAIS-IV MR	49.74	10.89	24-80		47.55	10.04	20-69	1.778	.077
WAIS-IV DS	47.21	10.04	26-80		43.21	9.14	24-70	3.542	<.001
WAIS-IV VP	51.59	10.19	10-72		47.31	9.84	28.74	3.597	<.001
WAIS-IV	47.69	9.51	24-70		45.11	8.94	19-70	2.346	.02
LNS									
WAIS-IV AR	46.56	10.31	22-77		42.6	9.44	16-64	3.411	<.001
TMT B	49.18	10.65	13-81		45.46	11.82	5-76	2.702	.007
FAS	48.5	10.21	26-85		46.5	11.75	27-86	1.475	.142
Animals	51.62	10.32	12-86		48.02	12.13	16-86	2.584	.011
CAPS-5 PTSD symptom score	18.27	13.76	0-53		30.36	14.77	0-72	-6.657	<.001
CAPS-5 PTSD diagnosis	27.92			60.2				29.66	<.001
ACC volume[d]	9057	1690	4532-13458		—	—	—		

Note. Yrs = Years; DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale; Current MDD Diagnosis= Major Depressive Disorder diagnosis based on the Structured Clinical Interview for DSM-5; WAIS-IV = Wechsler Adult Intelligence Scale - IV; SIM = Similarities; MR = Matrix Reasoning; DS = Digit Span; VP = Visual Puzzles; LNS = Letter Number Sequencing; AR = Arithmetic; TMT = Trail Making Test; FAS = Controlled Oral Word Association Test-FAS Phonemic Fluency; Animals = Animal Naming; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; ACC = Anterior Cingulate Cortex. [a]Active duty, reserve, and national guard are included within percentages for each branch. [b]A total of 8 participants were outside of the plausible score range (17-102) on the DRRI-2 and were removed from the descriptive values of combat exposure. [c] For point of reference, test performance data reflects demographically-adjusted T scores (Heaton 1981; Heaton et al., 2004; Tombaugh, 2004; Wechsler, 1997). [d] ACC volume includes bilateral ACC volume in cubic millimeters (rounded) not adjusted for overall intracranial volum

Table 2. Neuropsychological Test Raw Means, Standard Deviations, and Correlations

Variable	*M*	*SD*	1	2	3	4	5	6	7	8
1. SIM	26.41	4.54								
2. MR	17.54	4.89	.37							
3. DS	27.52	5.13	.26	.34						
4. LNS	19.59	2.99	.27	.41	.61					
5. VP	15.54	4.61	.32	.61	.35	.36				
6. AR	14.13	3.18	.37	.44	.49	.41	.44			
7. TMTB (R)	116.61	27.09	.28	.44	.41	.40	.40	.49		
8. FAS	41.51	11.42	.42	.30	.41	.33	.21	.36	.34	
9. Animals	22.68	5.07	.31	.31	.26	.28	.33	.28	.27	.56

Note. N = 234. M and SD are used to represent mean and standard deviation, respectively. Reverse-scored items are denoted with an (R). Values in square brackets indicate the 95% confidence interval. All correlations are significant at $p < .01$. MR = Matrix Reasoning; VP = Visual Puzzles; SIM = Similarities; TMT B = Trail Making Test B; AR = Arithmetic; DS = Digit Span; LNS = Letter Number Sequencing; Animals = Animal Semantic Fluency; FAS = Controlled Oral Word Association Test-FAS Phonemic Fluency.

Table 3. Executive Functioning Factor Loadings

	Factor Loadings	
	1	**2**
Factor 1: Cognitive Flexibility (CF)		
MR	**0.90**	-0.14
VP	**0.77**	-0.07
SIM	**0.41**	0.08
TMTB (R)	**0.39**	0.29
AR	**0.37**	0.36
Factor 2: Working Memory (WM)		
DS	-0.18	**0.98**
LNS	0.07	**0.65**

Note. *N* = 234. The extraction method was principal axis factoring with an oblique (Promax) rotation. Reverse-scored items are denoted with an (R). MR = Matrix Reasoning; VP = Visual Puzzles; SIM = Similarities; TMT B = Trail Making Test B; AR = Arithmetic; DS = Digit Span; LNS = Letter Number Sequencing.

Table 4. Raw Means, Standard Deviations, and Correlations for Variables of Interest and Potential Covariates for Executive Functioning Models

Variable	*M*	*SD*	1	2	3	4	5
1. DRRI-2	35.35	13.61					
2. CF	.06	9.13	-.06				
3. WM	-.1	9.11	-.11	.80**			
4. CAPS-5 symptom severity	18.27	13.75	.22**	-.03	-.11		
5. CAPS-5 diagnosis	32%	—	.18*	-.03	-.13	.77**	
6. MDD diagnosis	12%	—	-.01	-.09	-.07	.35**	.22**

Note. $N = 194$. M and SD are used to represent mean and standard deviation, respectively. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale; CF = Cognitive Flexibility factor; WM = Working Memory Factor; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5. * indicates $p < .05$. ** indicates $p < .01$.

Table 5. Parameter Estimates for EF Component Models with PTSD Symptom Severity as the Dependent Variable

	b	*95% CI* [UPPER, LOWER]	*p*	R^2
Model				**0.1707**
(Intercept)	8.32	-9.08, 26.37	0.355	
Age	-0.03	-0.24, 0.19	0.818	
Sex	6.83	0.47, 13.50	0.018	
Current MDD diagnosis	15.33	8.59, 21.75	<0.001	
Time since trauma	-0.00	-0.00, 0.00	0.855	
Years of education	-0.42	-1.36, 0.47	0.380	
Deployment TBI	0.77	-3.51, 5.14	0.723	
DRRI-2	0.22	0.06, 0.38	0.007	
CF	0.52	-0.37, 1.44	0.280	
WM	-0.24	-1.12, 0.63	0.596	
DRRI-2 x CF	-0.01	-0.03, 0.01	0.518	
DRRI-2 x WM	-0.00	-0.02, 0.02	0.921	

Note. N = 189. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale; WM = Working Memory Factor. Standard errors calculated based on 10,000 bootstrapped resamples.

Table 6. Parameter Estimates for EF Component Models with PTSD Diagnostic Status as the Dependent Variable

	OR	*95% CI* [UPPER, LOWER]	*p*	AUC
Model				**0.7242**
(Intercept)	0.19	0.00, 6.24	0.326	
Age	1.00	0.95, 1.04	0.884	
Sex	2.87	0.89, 10.18	0.039	
Current MDD diagnosis	5.15	1.89, 21.05	0.002	
Time since trauma	1.00	1.00, 1.00	0.748	
Years of education	0.90	0.72, 1.08	0.257	
Deployment TBI	0.92	0.33, 2.36	0.842	
DRRI-2	1.04	1.00, 1.08	0.027	
CF	1.10	0.93, 1.39	0.314	
WM	1.01	0.82, 1.20	0.922	
DRRI-2 x CF	1.00	0.99, 1.00	0.654	
DRRI-2 x WM	1.00	0.99, 1.00	0.336	

Note. N = 189. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale; WM = Working Memory Factor. Standard errors calculated based on 10,000 bootstrapped resamples.

Table 7. Raw Means, Standard Deviations, and Correlations for Variables of Interest and Potential Covariates for Anterior Cingulate Cortex Models

Variable	*M*	*SD*	1	2	3	4
1. DRRI-2	33.93	13.17				
2. CAPS-5 symptom severity	16.26	12.92	.23**			
3. CAPS-5 diagnosis	28%	—	.20*	.74**		
4. ACC	57.69	7.78	.10	.09	.12	
5. MDD diagnosis	12%	—	-.01	.32**	.19*	.04

Note. $N = 137$. M and SD are used to represent mean and standard deviation, respectively. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; ACC volume is adjusted for total intracranial volume and multiplied by 10000 for interpretability. * indicates $p < .05$. ** indicates $p < .01$.

Table 8. Parameter Estimates for Anterior Cingulate Cortex Models with PTSD Symptom Severity as the Dependent Variable

	b	*95% CI* [UPPER, LOWER]	*p*	R^2
Model				**0.1348**
(Intercept)	20.81	-34.66, 85.80	0.414	
Age	-0.13	-0.33, 0.07	0.215	
Deployment TBI	0.79	-4.06, 5.91	0.738	
Current MDD diagnosis	6.64	2.84, 10.30	<0.001	
DRRI-2	-0.31	-1.93, 1.15	0.657	
ACC volume	-0.25	-1.28, 0.64	0.553	
DRRI-2 x ACC volume	0.01	-0.02, 0.04	0.463	

Note. N = 137. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale. ACC volume is adjusted for total intracranial volume and multiplied by 10000 for interpretability. Standard errors calculated based on 10,000 bootstrapped resamples.

Table 9. Parameter Estimates for Anterior Cingulate Cortex Models with PTSD Diagnostic Status as the Dependent Variable

	OR	*95% CI* [UPPER, LOWER]	*p*	AUC
Model				**0.6837**
(Intercept)	0.17	0.00, 8725.56	0.733	
Age	0.98	0.93, 1.02	0.406	
Deployment TBI	0.93	0.31, 2.73	0.873	
Current MDD diagnosis	1.87	1.00, 3.99	0.03	
DRRI-2	0.98	0.72, 1.35	0.903	
ACC volume	0.99	0.83, 1.21	0.937	
DRRI-2 x ACC volume	1.00	1.00, 1.01	0.706	

Note. N = 137. DRRI-2 = Deployment Risk and Resilience Inventory-2 Combat Exposure subscale. ACC volume is adjusted for total intracranial volume and multiplied by 10000 for interpretability. Standard errors calculated based on 10,000 bootstrapped resamples.

APPENDIX A: ADJUSTMENTS TO DATA ANALYTIC PLAN

Adjustments to the initial analysis plan implemented to manage data access and availability challenges:

- Several measures originally planned for inclusion into the factor analyses were missing in the analytic dataset.
    - NIH List Sorting, which was hypothesized to be associated most strongly with the Working Memory factor
    - NIH Flanker, which was hypothesized to be associated most strongly with the Cognitive Flexibility/Inhibition factor
    - NIH Dimensional Change Card Sort, which was hypothesized to be associated most strongly with the Cognitive Flexibility/Inhibition factor

- To ensure adequate coverage of executive functioning skills and based on prior empirical work, additional measures available in the dataset were included:
    - WAIS-IV Arithmetic, which was hypothesized to be associated most strongly with the Working Memory factor
    - WAIS-IV Visual Puzzles, which was hypothesized to be associated most strongly with the Cognitive Flexibility/Inhibition factor
    - As noted above in the Discussion section, although these substitutions were the best available in the dataset, they may have resulted in inadequate coverage of the "inhibition" aspect of the hypothesized Cognitive Flexibility/Inhibition factor, leading us to name the factor "Cognitive Flexibility" only

- Additionally, analytic adjustments were made to accommodate unavailability of item or subtest-level data:
    - Medical Symptom Validity Test (MSVT): Indicator-level data was not available for this measure, and the MSVT as a whole was coded "yes" or "no" for below-threshold performance, with "yes" interpreted as indicating that performance was below clinical thresholds on at least one indicator. However, due to the unavailability of indicator-level data, below-chance performance was not able to be identified - in the absence of this information, an alternative validity criterion specified by the study, that is, below-threshold performance on at least one indicator of the MSVT, or above-threshold performance on the b Test, was used to identify individuals with atypical performance for exclusion from further analyses.
    - Deployment Risk and Resilience Inventory-2 (DRRI-2): Item-level data was not available for this measure. A small number of participants ($N = 8$) had scores out of the scoring range (17-102) for the DRRI-2 Combat Exposure subscale (score <17). As these scores were not plausible and no item-level data was available to perform re-scoring or assess for possible errors, participants whose scores fell below the lower bound of the measure were excluded from further analyses.

- Of 241 participants passing validity thresholds, a total of 232 participants were invited to the Neuroimaging visit. Unfortunately, beyond basic exclusionary medical contraindications (e.g., pregnancy, ferrous metal implants), no additional information is

available regarding study procedures for determining eligibility for the neuroimaging visit, resulting in nine additional individuals being excluded from the sample for unknown reasons.

APPENDIX B: COVARIATE TESTING FOR AIM 2 ANALYSES

Bivariate correlations between variables of interest and possible covariates were examined to determine covariates for inclusion in Aim 2 analyses involving executive functioning components:

Cognitive Flexibility was associated with years of education ($r = .15$, $p < .05$), inversely associated with age ($r = -.42$, $p < .01$) and time since trauma ($r = -.18$, $p < .01$), and was not associated with PTSD symptom severity or presence of PTSD diagnosis ($p > .05$). Working Memory was inversely associated with age ($r = -.31$, $p < .01$) and time since trauma ($r = .15$, $p < .01$), and was not associated with years of education ($r = .13$, $p > .05$), PTSD symptom severity ($r = -.11$, $p > .05$) or presence of PTSD diagnosis ($r = -.13$, $p > .05$). Combat exposure was significantly associated with sex ($r_{pb} = -.23$, $p < .01$), indicating that men reported greater combat exposure than females. Combat exposure was also significantly associated with the presence of deployment TBI ($r_{pb} = .51$, $p < .05$), PTSD symptom severity ($r = .22$, $p < .01$), and PTSD diagnosis ($r_{pb} = .18$, $p < .01$). In addition, the presence of an MDD diagnosis was significantly associated with both PTSD symptom severity ($r = .35$, $p < .01$) and the presence of a PTSD diagnosis ($r = .22$, $p < .01$).

Bivariate correlations between variables of interest and possible covariates were examined to determine covariates for inclusion in Aim 2 analyses involving ACC volume:

ACC volume (adjusted to reflect a ratio of ACC volume to total intracranial volume) was associated with age ($r = -.31$, $p < .01$) but not with combat exposure, PTSD symptom severity, or the presence of a PTSD diagnosis. MDD diagnosis was significantly correlated with PTSD symptom severity ($r = .32$, $p < .01$) and PTSD diagnostic status ($r = .19$, $p < .05$). Presence of deployment TBI significantly correlated with combat exposure ($r = .47$, $p < .01$).