The Brain at War:
Stress-Related Losses and Recovery-Related Gains

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt,

• dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,

• dass ich mich nicht bereits anderwärts um einen Doktorgrad beworben habe und keinen Doktorgrad in dem Promotionsfach Psychologie besitze, und

• dass ich die zugrunde liegende Promotionsordnung vom 5. Marz 2015 kenne.

Berlin, den ……

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Summary

Stress is an unavoidable part of life and the stress response is often highly adaptive. However, under conditions of extreme or chronic stress, the stress response can become maladaptive and can negatively impact the brain, behavior, and cognition. Combat exposure is a specific instantiation of prolonged stress, and one that is growing in relevance due to an increasing number and escalating intensity of military conflicts across the globe. In this dissertation, I investigate stress-related losses and recovery-related gains in gray matter volume, mainly in combat-exposed military populations.

The present dissertation contributes to knowledge about the relationship between stress and the brain in four ways: (a) it investigates the relationship between stress exposure and the brain in subclinical populations, (b) it investigates potential functional mechanisms for the development and maintenance of combat-related posttraumatic stress disorder (PTSD), (c) it investigates alterations in grey matter volume following therapeutic interventions for combat-related PTSD, and (d) it investigates the neural correlates of symptom exaggeration in PTSD.

The dissertation is publication-orientated and consists of six papers. At the time of submission, *Paper I, Paper II, Paper III and Paper IV* have been published. *Paper V* and *Paper VI* have been submitted and are currently under review.

Paper I assesses grey matter reductions related to military deployment in a subclinical population, using structural neuroimaging. Results show that duration of deployment correlates with smaller prefrontal gray matter in the ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC), regions traditionally observed to be reduced in PTSD populations.

Paper II seeks to replicate the findings of *Paper I* by assessing neural correlates of exposure to community violence exposure in a civilian adolescent population. Results show that higher rates of community violence exposure correlate with smaller prefrontal gray matter volume, specifically in the vmPFC and ACC.

Paper III explores potential factors underlying the development and maintenance of PTSD by assessing combat-exposed individuals with and without PTSD using an emotion regulation paradigm and functional neuroimaging. Two emotion regulation strategies, cognitive reappraisal and expressive suppression, were compared. Results indicate that when instructed to cognitively reappraise trauma-related stimuli, individuals with PTSD may instead rely on expressive suppression to regulate negative emotion.

Paper IV is a pilot structural neuroimaging study investigating changes in gray matter

volume following a traditional psychotherapeutic intervention for PTSD. Individuals with combat-related PTSD were assessed prior to and following psychotherapy and compared to a waiting-list control group. Results show that hippocampal gray matter volume increased in the therapy group, compared to the control group, following therapy.

Paper V again investigates changes in gray matter volume, this time examining a novel therapeutic intervention for PTSD. Individuals with combat-related PTSD were assessed prior to and following psychotherapy. The control group completed eye movement desensitization and reprocessing (EMDR) therapy, a typical treatment for PTSD, while the experimental group completed a video gaming intervention, playing Tetris for 60 minutes per day in addition to psychotherapy. Individuals who played Tetris showed increases in hippocampal volume compared with the control group following completion of therapy. In addition, increases in hippocampal volume were related to decreases in psychological symptoms at a six-month follow-up assessment in the experimental group, but not in the control group.

Paper VI investigates the neural correlates of malingering, or symptom simulation or exaggeration, in PTSD. Individuals with a current diagnosis of combat-related PTSD were assessed with structural neuroimaging prior to onset of therapy. Participants were classified as either credible patients or as malingerers based on their performance on a symptom validity test (SVT). Individuals identified as malingerers showed larger gray matter volumes than credible patients in regions involved in PTSD, inhibition, and deception.

In summary, the current dissertation contributes to research on stress and the brain in several ways. The key insights gained from this dissertation are that stress exposure correlates with smaller prefrontal gray matter volumes, also in subclinical populations, military and civilian, adult and adolescent. It provides initial evidence of the neural processes underlying psychological factors related to the development and maintenance of stress-related symptomatology. Trauma-exposed individuals with and without PTSD differ at a neural and behavioral level in their ability to regulate negative emotion, presenting a novel insight into the etiology of PTSD. This dissertation also provides first evidence of increases in the hippocampus following psychotherapy for PTSD, and of the efficacy of a novel video gaming therapeutic intervention at the brain and symptom levels. Finally, it presents evidence for structural differences between malingerers and credible PTSD patients, indicating that SVTs should be incorporated into future studies to ensure robustness of clinical populations.

Zusammenfassung

Stress ist Teil unseres Lebens und unsere Stressreaktion oft adaptiv. Unter extremen Bedingungen oder chronischem Stress kann diese Stressantwort jedoch maladaptiv werden und das Gehirn, Verhalten und Kognition negativ beeinflussen. Die Erfahrung von militärischen Kampfeinsatz ist eine spezifische Form von anhaltendem Stress, die aufgrund einer zunehmenden Anzahl und zunehmender Intensität militärischer Konflikte auf der ganzen Welt an Bedeutung gewinnt.

In der vorliegenden Dissertation untersuche ich stressbedingte Verluste und erholungsbedingte Gewinne der grauen Hirnsubstanz, hauptsächlich in militärischen Populationen. Diese Dissertation trägt auf vier Wegen zum Wissen über die Beziehung zwischen Stress und Gehirn bei: Sie untersucht (a) den Zusammenhang zwischen Stressbelastung und Gehirn in subklinischen Populationen, (b) mögliche funktionelle Mechanismen für die Entwicklung und Aufrechterhaltung von Posttraumatischer Belastungsstörung (PTBS) bedingt durch militärischen Einsatz, (c) Veränderungen im Volumen der grauen Substanz nach therapeutischen Interventionen für einsatzbedingte PTBS, und (d) die neuronalen Korrelate der Symptomübertreibung in PTBS.

Die Dissertation ist publikationsorientiert und besteht aus sechs Artikeln. Zum Zeitpunkt der Einreichung sind *Artikel I*, *Artikel II*, *Artikel III* und *Artikel IV* veröffentlicht. *Artikel V* und *Artikel VI* wurden eingereicht und werden derzeit überprüft.

In *Artikel I* werden Reduktionen der grauen Substanz im Zusammenhang mit militärischem Einsatz in einer subklinischen Population unter Verwendung struktureller Bildgebung untersucht. Die Ergebnisse zeigen, dass die Einsatzdauer mit weniger grauer Substanz im ventromedialen präfrontalen Kortex (vmPFC) und dem anterioren cingulären Kortex (ACC) korreliert; Regionen, die bei PTBS-Populationen traditionell reduziert sind.

In *Artikel II* wird versucht, die Ergebnisse von *Artikel I* zu replizieren, indem neuronale Korrelate der Exposition von Gewalt bei Jugendlichen untersucht werden. Die Ergebnisse zeigen, dass höhere Gewaltexposition mit weniger Volumen der präfrontalen grauen Substanz korreliert, insbesondere im vmPFC und ACC.

In *Artikel III* werden mögliche Faktoren untersucht, die der Entwicklung und dem Erhalt von PTBS zugrunde liegen. Hier werden Personen mit oder ohne PTBS mit einem Emotionsregulationsparadigma und funktioneller Magnetresonanztomographie (fMRT) untersucht. Zwei Strategien zur Emotionsregulation, kognitive Neubewertung und expressive Unterdrückung, wurden verglichen. Die Ergebnisse zeigen, dass Personen mit PTBS, die

aufgefordert wurden, Trauma-bezogene Stimuli kognitiv neu zu bewerten, eher expressive Unterdrückung benutzen, um negative Emotionen zu regulieren.

Artikel IV ist eine Pilotstudie, welche Veränderungen in der grauen Substanz nach einer psychotherapeutischen Intervention für PTBS untersucht. Individuen mit PTBS bedingt durch militärischen Einsatz wurden vor und nach einer Psychotherapie untersucht und mit einer Wartelisten-Kontrollgruppe verglichen. Die Ergebnisse zeigen, dass das Volumen der grauen Substanz im Hippocampus in der Therapiegruppe verglichen zur Kontrollgruppe anstieg.

In *Artikel V* werden Veränderungen des Volumens der grauen Substanz untersucht, wobei diesmal eine neuartige therapeutische Intervention für PTBS untersucht wird. Personen mit militärisch bedingter PTBS wurden vor und nach einer Psychotherapie untersucht. Die Kontrollgruppe schloss die für die PTBS typische Behandlung der Augenbewegungsdesensibilisierung und Verarbeitung (EMDR) ab, während die Experimentalgruppe eine Videospiel Intervention absolvierte und Tetris 60 Minuten pro Tag zusätzlich zur Psychotherapie spielte. Individuen, die Tetris spielten, zeigten einen Anstieg des Hippocampusvolumens verglichen mit der Kontrollgruppe nach Beendigung der Therapie. Darüber hinaus konnte ein Anstieg des Hippocampusvolumens mit einem Rückgang der psychologischen Symptome bei einer sechsmonatigen Nachuntersuchung in der Experimentalgruppe in Verbindung gebracht werden, jedoch nicht in der Kontrollgruppe.

In *Artikel VI* werden die neuronalen Korrelate von Simulations- oder Symptom-Simulationen oder Übertreibungen bei PTBS untersucht. Personen mit einer aktuellen Diagnose einsatzbezogener PTBS wurden vor Beginn der Therapie mit strukturellen MRT-Verfahren getestet. Die Teilnehmer wurden basierend auf ihren Antworten in einem Symptomvaliditätstest (SVT) entweder als glaubwürdige Patienten oder als Simulanten klassifiziert. Individuen, die als Simulanten identifiziert wurden, zeigten größere graue Substanzvolumina als glaubwürdige Patienten in Regionen, die bei PTSD, Inhibition und Täuschung involviert sind.

Zusammenfassend trägt die vorliegende Dissertation in mehrfacher Hinsicht zur Erforschung von Stress und seine Auswirkungen auf das Gehirn bei. Die wichtigsten Erkenntnisse aus dieser Dissertation sind, dass die Stressbelastung mit kleineren Volumina der präfrontalen grauen Substanz korreliert ist, auch in subklinischen Populationen, militärischen und zivilen, Erwachsenen, sowie Jugendlichen. Sie liefert erste Hinweise auf die neuralen Prozesse, die psychologischen Faktoren im Zusammenhang mit der Entwicklung und Aufrechterhaltung von stressbedingter Symptomatik zugrunde liegen. Trauma-exponierte

Individuen mit und ohne PTBS unterscheiden sich auf neuronaler und Verhaltensebene in ihrer Fähigkeit, negative Emotionen zu regulieren, was einen neuen Einblick in die Ätiologie von PTBS bietet. Darüber hinaus liefert die vorliegende Dissertation erste Evidenz für einen Anstieg des Hippocampusvolumens nach einer Psychotherapie für PTBS und demonstriert die Wirksamkeit einer neuartigen therapeutischen Videospiel Intervention sowohl auf neurobiologischer, als auch verhaltensbasierter Ebene. Schließlich liefert sie Evidenz für strukturelle Unterschiede zwischen Simulanten und glaubwürdigen PTBS-Patienten, welche die Integration von SVTs in zukünftigen Studien nahelegt, um die Robustheit klinischer Populationen sicherzustellen.

List of Original Papers

Paper I

Butler, O., Adolf, J., Gleich, T., Willmund, G., Zimmermann, P., Lindenberger, U., Gallinat, J., Kühn, S. (2017). Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population. *Translational Psychiatry*, doi: 10.1038/tp.2016.288

Paper II

Butler, O., Yang, X. F., Laube, C., Kühn, S., Immordino-Yang, M. H. (2018). Community Violence Exposure Correlates with Smaller Gray Matter Volume and Lower IQ in Urban Adolescents. *Human Brain Mapping*, doi: 10.1002/hbm.23988

Paper III

Butler, O., Willmund, G. , Gleich, T., Zimmermann, P., Lindenberger, U., Gallinat, J., Kühn, S. (2018). Cognitive reappraisal and expressive suppression of negative emotion in combat-related posttraumatic stress disorder: A functional MRI study. *Cognitive Therapy and Research,* doi: 10.1007/s10608-018-9905-x

Paper IV

Butler, O., Willmund, G., Gleich, T., Gallinat, J., Kühn, S., Zimmermann, P. (2018). Hippocampal gray matter increases following psychological treatment for combat-related posttraumatic stress disorder. *Brain and Behaviour*, doi: 10.1002/brb3.956

Paper V

Butler, O., Herr, K., Willmund, G., Gallinat, J., Kühn, S., Zimmermann, P. (under review). Trauma, Treatment and Tetris: Video gaming increases hippocampal volume in combat-related posttraumatic stress disorder.

Paper VI

Butler, O., Herr, K., Willmund, G., Gallinat, J., Zimmermann, P., Kühn, S. (under review). Neural correlates of malingering: Larger hippocampal volume correlates with symptom aggravation in combat-related posttraumatic stress disorder.

List of Abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
CAT	Computational anatomy toolbox
CBT	Cognitive behavior therapy
DSM	Diagnostic and statistical manual of mental disorders
EMDR	Eye movement desensitization and reprocessing
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
MRI	Magnetic resonance imaging
MENT	Morel emotional numbing test
PTSD	Posttraumatic stress disorder
ROI	Region of interest
SPM	Statistical parameter mapping
SSRI	Selective serotonin reuptake inhibitor
SVT	Symptom validity test
VBM	Voxel based morphometry
vmPFC	Ventromedial prefrontal cortex

Table of Contents

1. Introduction

Neuroimaging research into the effects of stress on the human brain has mainly focused on PTSD. This research has been highly fruitful and has contributed greatly to our understanding of PTSD specifically, and stress more generally. However, some key points remain unclear. First, trauma-exposed individuals without a diagnosis of PTSD have often served as controls, and the effects of stress exposure at the subclinical level have mainly been overlooked. Second, only a minority of trauma-exposed individuals will go on to develop the persistent and debilitating symptoms that characterize PTSD, but functional and behavioral factors that underlie either recovery from or maintenance of symptoms remain to be fully elucidated. Third, it remains unclear if the smaller gray matter volumes typically observed in PTSD populations resolve following therapeutic interventions. Fourth, although PTSD symptoms are prone to simulation or exaggeration, no neuroimaging study to date has investigated the neural correlates of symptom exaggeration in PTSD.

In my dissertation, I aim to advance the field of stress and PTSD neuroimaging by investigating the structural correlates of stress exposure in subclinical populations, functional and behavioral differences between clinical and subclinical populations, increases in gray matter volume following therapeutic interventions for PTSD, and the neural correlates of symptom exaggeration in PTSD. I will first outline the theoretical and empirical background of my work. Following this, I will give a brief summary of each of the papers arising therefrom. Finally, results and implications of my work are discussed, along with limitations and directions for future research.

2. Theoretical and Empirical Foundations

2.1. Concepts of Stress

Stress and the stress response

Stress is an integral part of everyday life, and the negative effects of stress are widely recognized, both in scientific literature and in society more broadly. When discussing stress, it is important to distinguish between cause and effect, between stressors and the stress response. Broadly speaking, a stressor is anything that interferes with an organism's homeostatic equilibrium, while the stress response is the organism's attempt to return to a state of balance, via homeostatic and allostatic changes (Cannon, 1935; McEwen & Wingfield, 2003). At a psychological level, stress is said to be experienced when the demands of the environment outstrip the individual's perceived ability to cope with these demands (Lazarus & Folkman, 1984). At an endocrinological level, the stress response is characterized by the release of adrenaline, noradrenaline, and corticoids via activation of the adrenal glands and the hypothalamic-pituitary-adrenal (HPA) axis. At a physiological level, the release of these hormones leads to activation of the sympathetic branch of the autonomic nervous system and suppression of the parasympathetic branch. There is then a rapid release of glucose into the blood stream, heart rate and blood pressure rise, and blood flow is directed away from the internal organs towards the large skeletal muscles. Salivation and digestion are inhibited, as are immunology and reproduction. Long-term growth and repair is suppressed in favor of the rapid mobilization of resources to attend to the immediate threat.

This "fight or flight" response is remarkably conserved across species and scenarios (Cannon, 1932; Sapolsky, 2004). Similar changes in hormone levels and physical arousal occur whether the stressor is physical or psychosocial, and also whether it is current or anticipated (Sapolsky, 2004). However, the stress response has evolved to most effectively deal with acute physical stressors of the type that will strongly affect individuals'

reproductive fitness, such as hunting prey or being attacked. However, the types of chronic, anticipated or psychosocial stressors that characterize the majority of stressful events in modern human society are relatively new developments, and ones to which the stress response has not yet had time to adapt. Rather, the same response preparing us for a sudden burst of physical activity, a fight or a flight, is activated whether we worry about owing money to a loan shark or are swimming away from a great white.

Adaptivity and disease

The suppression of the parasympathetic nervous system, and the inhibition of immunology, digestion, growth, repair, and reproduction makes perfect sense when faced with a sudden physical threat requiring an immediate response. To quote Sapolsky, "if the lion's on your tail, two steps behind you, worry about ovulating . . . some other time" (2004, page 11). However, if the stress response is chronically activated, it can become more damaging than the stressor itself, particularly if the stress is merely anticipated or psychological. This is because the body continues to direct resources for a burst of physical activity that never comes, rather than on its long-term projects, such as the production of T-cells (Herbert & Cohen, 1993) and sperm (McGrady, 1984; Nargund, 2015).

Psychological and social stress are known to have negative impacts on physical health in humans, increasing the risk of coronary heart disease (Krantz & McCeney, 2002; Strike & Steptoe, 2004) and peptic ulcers (Levenstein, Rosenstock, Jacobsen, & Jorgensen, 2015) as well as negatively influencing health behaviors (Adler & Matthews, 1994; Oliver, Wardle, & Gibson, 2000). In addition, stress is related to increased risk for psychiatric disorders including depression, anxiety, and substance abuse (Dohrenwend, 2000; Meyer, 2003).

One should note that these negative effects on psychological and physical health are associated with chronic rather than acute stress. Indeed, there is evidence that acute stress can be beneficial, and can increase hippocampal neurogenesis (Kirby et al., 2013) and hippocampal function, including learning and memory (Diamond, Bennett, Fleshner, & Rose,

1992). In addition, mild stressors, such as exercise and caloric restriction, may also protect the brain in aging, and have been shown to improve memory and reduce the risk of dementia in older age (Larson et al., 2006; Witte, Fobker, Gellner, Knecht, & Flöel, 2009). In sum, not all forms of stress are harmful. In my work, however, I focus on the negative effects of chronic stressors on the brain, behavior, and cognition, rather than the positive or protective effects of acute stressors.

Animal models of stress

Animal models provide a compelling approach for the study of stress because of similarities in the stress response across mammals. In addition, animal studies allow for the experimental manipulation of environmental, neural, genetic and endocrinological factors not possible in humans, due to practical and ethical considerations. Animal models have long been applied to convincingly demonstrate the negative effects of stress on the brain, behavior, and cognition (Cannon, 1914; Selye, 1936). At a neural level, chronic stress, or its simulation via the administration of glucocorticoids, has been shown to produce reductions in brain volume, particularly in the hippocampus, through dendritic atrophy, reductions in neurogenesis, and by making neurons more susceptible to death from environmental insults (Sapolsky, 1992; Sapolsky, Krey, & McEwen, 1985; Sapolsky, Uno, Rebert, & Finch, 1990). At a cognitive level, chronic stress has been shown to impair learning and memory, including fear extinction (de Quervain, Roozendaal, & McGaugh, 1998; Miracle, Brace, Huyck, Singler, & Wellman, 2006). At a behavioral level, chronic stress has been shown to produce depression- and anxiety-like symptoms including freezing, reduced exploration, and decreased social and sexual behavior (Blanchard, McKittrick, & Blanchard, 2001; D'Aquila, Brain, & Willner, 1994; Katz, Roth, & Carroll, 1981; Lupien, McEwen, Gunnar, & Heim, 2009; Willner, 1997). In addition, chronic stress has been linked to increases in substance use and lower thresholds for addiction (Wand, 2008). However, as the complexity of the construct under observation increases, the utility of animal studies may decrease. For example, the relationship between

stress exposure and complex clinical constructs such as PTSD in animal models remains unconvincing (Flandreau & Toth, 2017; Goswami, Rodríguez-Sierra, Cascardi, & Paré, 2013; Steimer, 2011).

2.2. Posttraumatic Stress Disorder

Etiology

Neuroscientific research into the effects of stress on the adult human brain has mainly focused on PTSD, which is almost unique among psychiatric disorders because a clear etiological event, i.e., exposure to extreme stress or trauma, is a key diagnostic criterion. It is estimated that up to 90% of individuals will be exposed to trauma in their lifetime (Kilpatrick et al., 2013), with around a third of individuals experiencing four or more traumatic events (Benjet et al., 2016). Psychological distress is common in the period directly following a traumatic event and is not considered pathological. Indeed, the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV states that symptoms of hyperarousal, avoidance, numbing, and intrusions must be present for more than one month to qualify for a diagnosis of PTSD (American Psychiatric Association, 2013). Thus, what distinguishes a normal from a pathological stress response are not the psychological or behavioral correlates, but rather their duration. In the majority of cases, symptoms will gradually resolve in the days and weeks following exposure. However, a significant subset of individuals will go on to develop the persistent and debilitating symptoms that characterize PTSD.

Lifetime prevalence rates of PTSD stand at around 8% in adults in western populations, but vary depending on the individual's gender, age, education, and previous history of trauma (Brewin, Andrews, & Valentine, 2000; Kilpatrick et al., 2013). Lifetime prevalence for PTSD is twice as high for women (10.4%) as for men (5%) and women are four times more likely to develop PTSD following the same traumatic event (Foa, Keane, & Friedman, 2000). It is known that levels of gonadal hormones influence the brain, with

changes in brain structure and function observed between females at different stages in menstrual cycle (Lisofsky, Mårtensson, et al., 2015; Lisofsky, Lindenberger, & Kühn, 2015), and how the brain responds to stress, leading to different effects of stress between males and females (McEwen, 2010; McEwen & Morrison, 2013). However, females are also more likely to experience certain types of trauma that are associated with an increased risk of PTSD, such as interpersonal violence and sexual assault (Brewin et al., 2000; Kaminer, Grimsrud, Myer, Stein, & Williams, 2008; Kilpatrick et al., 2003). As such, gender differences in prevalence may reflect a combination of biological and sociocultural factors.

Younger, less educated persons with a previous history of trauma are also known to be at increased risk for PTSD (Alisic et al., 2014; Breslau, Chilcoat, Kessler, & Davis, 1999; Brewin et al., 2000). Higher age and education may equip an individual with greater resources to cope with stress and provide greater resilience, while a previous history of trauma may reduce an individual's ability to manage with current stress. There is evidence that stress and trauma exposure may act cumulatively at both the neural and psychological levels, and thereby reduce resilience. A dose–response relationship has also been observed in PTSD, with higher rates of trauma exposure correlating with increased incidence (Neuner et al., 2004). In addition, stress is known to negatively affect the structure and function of the hippocampus, a key region involved in learning and memory (Eichenbaum, 2004; Squire, Stark, & Clark, 2004).

Smaller hippocampal volumes are thought to represent a risk factor for the development of PTSD (Gilbertson et al., 2002), which is characterized by dysfunction in memory and negative alterations in cognition. As such, previous trauma exposure may reduce hippocampal function and increase the risk of developing PTSD-like symptoms following new trauma, although the precise mechanisms underlying the relationship between smaller hippocampal volume and increased risk for PTSD remain unclear.

Diagnostic criteria and symptoms

PTSD is a debilitating psychiatric disorder characterized by symptoms of hyperarousal, avoidance, numbing, intrusions, and negative alterations in mood and cognition. Diagnosis of PTSD is made by clinical assessment of the stress or trauma experienced, including the type, frequency, and duration, the intensity of experienced symptoms, and the level of functional impairment caused by the symptoms (American Psychiatric Association, 2013).

PTSD was first formalized as a clinical diagnosis in the 1980s, when it was added to the DSM-III (American Psychiatric Association, 1980). Since then, recognition of PTSD by clinicians has increased to the point where it is now the third most commonly diagnosed disorder by psychologists (Evans et al., 2013).

Emotion regulation

At a psychological level, one reason for the failure of symptoms to resolve over time may be the use of ineffective or maladaptive strategies to regulate the negative emotions that arise following trauma. A cognitive model of PTSD (Ehlers & Clark, 2000) proposes that maladaptive processing of trauma and its sequelae leads to an ongoing sense of serious, current threat, an appraisal which encourages "individuals to engage in dysfunctional coping strategies that have the paradoxical effect of enhancing PTSD symptoms" (Ehlers & Clark, 2000). One such dysfunctional process is the regulation of emotion, specifically the down-regulation or reduction of negative emotion. According to a process model of emotion regulation (Gross, 1998, 2002), strategies differ in where they target along the timeline of an unfolding emotional response. Strategies also vary in the cognitive processes they employ and their effectiveness. At the broadest level, emotion regulation can be divided into antecedent- and response-focused strategies. Antecedent-focused strategies aim to alter an emotional response before it occurs, such as through reinterpreting the meaning or context of a stimulus, as in situation-focused cognitive reappraisal, or by modifying one's perspective, as in self-focused cognitive reappraisal (Ochsner et al., 2004; Willroth & Hilimire, 2016). In contrast,

response-focused strategies aim to alter a response once it has already occurred, for example by suppressing the physical expression of emotion. However, it has long been noted that attempting to suppress a thought has the paradoxical effect of creating preoccupation with that thought and making it more likely to occur (Freud, 1914; Lazarus, 1983; Wegner, 1994).

Shifting from suppression to reappraisal-based emotion regulation strategies has been associated with improvements in treatment outcomes (Price, Monson, Callahan, & Rodriguez, 2006) and difficulties with emotion regulation were found to partially mediate the relationship between PTSD and related comorbidities (Klemanski, Mennin, Borelli, Morrissey, & Aikins, 2012). In a study by Shepherd and Wild (2014), PTSD patients and trauma-exposed controls were instructed to feel, maintain, or decrease their emotional response to negative and neutral images. PTSD symptoms were associated with greater spontaneous use of suppression and less use of reappraisal (Shepherd & Wild, 2014). A prospective study by Boden and colleagues (2013) assessed use of emotion regulation strategies and symptom severity in combat veterans with PTSD prior to and following therapy. Use of suppression was associated with more symptoms, while use of reappraisal was associated with fewer symptoms at both time points. Following therapy, use of suppression decreased and use of reappraisal increased, and shifting from suppression to reappraisal predicted reductions in symptom severity (Boden et al., 2013). As such, a better understanding of the use of emotion regulation strategies in PTSD, in particular expressive suppression, may offer key insights into the etiology and treatment of PTSD.

Therapeutic interventions: Psychotherapy

The most widely used and also most effective interventions for PTSD are psychotherapies, such as trauma-focused cognitive behavior therapy (CBT) and EMDR (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013). These therapies target memories of the traumatic event, along with the individual's cognitive and emotional interpretation of the event (Butler, Chapman, Forman, & Beck, 2006). EMDR is particularly interesting as it is a relatively new

therapeutic method (Shapiro, 1989a, 1989b, 1996), which differs from other psychotherapies by incorporating a visuosensory attentional component. There are some inconsistencies in the literature regarding EMDR, particularly the therapeutic contribution of the visuosensory component (Seidler & Wagner, 2006); while reviews of studies comparing trauma-focused CBT and EMDR have failed to demonstrate increased efficacy for one over the other (Bisson et al., 2013; Seidler & Wagner, 2006), separate reviews have provided evidence that the addition of eye movements results in significant improvements to treatment outcomes (Jeffries & Davis, 2013; Lee & Cuijpers, 2013). As such EMDR provides an effective therapeutic intervention, although the precise mechanisms underlying this efficacy remain somewhat unclear.

During an EMDR session, the patient is asked to focus on the traumatic memory, along with all accompanying emotional sensations, and to make brief statements about their beliefs or feelings about the event (Shapiro, 1989a). In addition, the patient is asked to simultaneously attend to an alternating bilateral stimulus. Originally this involved engaging in periodic eye movements by attending to a moving visual stimulus controlled by the therapist (Shapiro, 1989a), but has now expanded to include auditory and tactile stimuli (Seidler & Wagner, 2006). Furthermore, maladaptive, destructive cognitions are identified, edited and corrected, and replaced by constructive cognitions.

Therapeutic interventions: Pharmacology

Pharmacological treatments are also available for PTSD. However, reviews of the literature have failed to show strong evidence of differences between psychotherapy, pharmacology or a combination of both on treatment outcomes (Hetrick, Purcell, Garner, & Parslow, 2010), although selective serotonin reuptake inhibitors (SSRI), such as paroxetine, have been shown to have a small positive impact compared with placebo (Hoskins et al., 2015; Puetz, Youngstedt, & Herring, 2015). However, the biological or neural mechanisms by which medications improve PTSD symptoms are unclear. One possibility is that antidepressants may

target one of the key brain regions implicated in PTSD, the hippocampus, as treatment with SSRIs has been shown to increase hippocampal neurogenesis (Anacker et al., 2011). In addition, long-term treatment with the SSRI paroxetine has been shown to correlate with increases in hippocampal volume and improvements in memory performance in PTSD (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003).

Therapeutic interventions: Outcomes

At a broader level, PTSD currently has a poor long-term prognosis. The majority of individuals will continue to experience symptoms for months or even years after initial diagnosis, with a median remission time of three years for individuals who seek professional treatment, and nearly double that for individuals who do not (Kessler, 1995). In addition, some individuals will never fully recover, with PTSD failing to remit in up to one third of individuals, regardless of whether they seek therapy or not (Kessler, 1995). In the more immediate term, a significant portion of individuals fail to show improvements in symptoms even directly following therapy, with some studies showing nonresponse rates of up to 50% (Bisson et al., 2013; Bradley, Greene, Russ, Dutra, & Westen, 2005; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). As such, novel treatments are required to improve both short and long-term outcomes in PTSD.

Novel therapeutic interventions: Brain volume

As summarized above, psychotherapeutic and pharmacological interventions have been shown to be effective in specific contexts, for example in the short-term, or compared to placebo. However, substantial room for improvement remains. One particularly promising route is the development of additional or adjunct interventions that may support or scaffold established therapies. To effectively test the utility of novel standalone interventions, individuals with distressing and debilitating psychological symptoms are prevented from accessing forms of therapy that are partially effective, in favor of novel interventions of undetermined efficacy and effectiveness. This approach necessarily brings with it multiple

practical and ethical concerns, which are avoided if the novel intervention can be administered in combination with existing therapies.

One potential target for novel interventions is the hippocampus. As previously mentioned, pharmacological interventions have been shown to increase hippocampal volume in PTSD and increases in hippocampal volume correlated with improvements in memory and reductions in symptoms (Levy-Gigi, Szabó, Kelemen, & Kéri, 2013; Vermetten et al., 2003). However, pharmacological interventions are also associated with significant adverse physical effects, such as weight gain, nausea, and dry mouth (Fava, 2000; Ferguson, 2001; Serretti & Mandelli, 2010; Uher et al., 2009), often leading to noncompliance. In addition, pharmacological interventions can be expensive; as a trained clinician is required to prescribe and monitor the administration of medication, and the drugs themselves can be prohibitively expensive.

Hippocampal volume has also been shown to increase via training interventions, including spatial memory (Woollett & Maguire, 2011), video gaming (Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014), and exercise (Erickson et al., 2011). Indeed, initial evidence suggests that exercise may improve PTSD symptoms (Manger & Motta, 2005), although prospective or longitudinal research in this field is sorely lacking. If increases in hippocampal volume are the therapeutic mechanism by which SSRIs aid in the recovery of PTSD, then non-pharmacological interventions which similarly target the hippocampus may also offer a powerful novel therapeutic intervention. Additionally, training interventions also represent an important improvement on current pharmacological treatments due to reduced costs and lack of side effects.

Novel therapeutic interventions: Tetris

Recent work has provided initial evidence of the video game Tetris as a preventative cognitive intervention to reduce intrusive memories following trauma. Holmes and colleagues have demonstrated in both experimental (Holmes, James, Coode-Bate, & Deeprose, 2009;

Holmes, James, Kilford, & Deeprose, 2010) and real-world settings (Horsch et al., 2017; Iyadurai et al., 2017) that playing Tetris directly following trauma exposure can reduce the subsequent number and intensity of trauma-related memories. Specifically, Tetris playing reduces unwanted, intrusive memories, similar to flashbacks in PTSD, but does not impair voluntary memory, such as recognition (Holmes et al., 2009).

Memory formation is not an immediate, automatic, or infallible process. Rather, following an event, the memory trace for the event must be consolidated into long-term memory to make it available for long-term recall (McGaugh, 2000). During the period of memory consolidation, estimated to be approximately six hours, the memory remains in a labile state and is vulnerable to interference (Wixted, 2004). Performing an unrelated task while memory for an event is in this labile state can reduce subsequent retrieval (Walker, Brakefield, Hobson, & Stickgold, 2003). It is hypothesized that completing a demanding visuospatial task following trauma exposure weakens the strength of the traumatic memory via retroactive interference. Specifically, Tetris playing is thought to weaken consolidation of the visuosensory elements of the memory trace due to competition for cognitive resources (James, Lau-Zhu, Tickle, Horsch, & Holmes, 2016).

To date, work using Tetris as an intervention has focused on attempting to disrupt consolidation of the traumatic memory, either within the first six hours (Holmes et al., 2009, 2010; Horsch et al., 2017; Iyadurai et al., 2017) following the trauma exposure, or the next day (James et al., 2015). However, playing a video game in the direct aftermath of a traumatic event is neither practical nor possible in every case. In addition, no study to date has assessed the effects of playing Tetris on individuals with existing PTSD. Therefore, studies investigating the utility of Tetris as an adjunct therapeutic intervention for individuals with current PTSD are of great potential interest.

Tetris may be particularly suitable as an adjunct intervention, in combination with psychotherapies such as EMDR. In order to disrupt consolidation, a traumatic memory must

be in a labile state, either because it is in the period of initial consolidation following the event, or because it is being reconsolidated following reactivation (James et al., 2015). During a trauma-focused psychotherapy session the individual is asked to reactivate the traumatic memory, as well as the corresponding emotional response. Therefore, the period immediately following the therapy session provides a perfect time window to target and weaken the reconsolidation of the traumatic memory by playing Tetris. One possible concern is that Tetris could also reduce memories of the constructive cognitions established during the therapy session. However, it should be noted that playing Tetris has been shown to reduce the vivid, intrusive elements of a traumatic memory, but not declarative memory (Holmes et al., 2009). As such, Tetris should not interfere with the clinical efficacy of EMDR.

2.3. Stress and the Brain

Neuroimaging research on posttraumatic stress disorder

PTSD populations demonstrate alterations in the function and structure of the brain, particularly in regions involved in cognition, fear, and memory, including the medial-prefrontal cortex, the amygdala, and the hippocampus.

At a structural level, PTSD is associated with smaller regional gray matter volumes, particularly in the hippocampus and the medial prefrontal cortex, including the vmPFC and ACC (Karl et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Kühn & Gallinat, 2013; Smith, 2005). A role for these regions in PTSD symptomatology is supported by their well-established roles in memory formation (Squire, 1992), emotion regulation (Carter, Botvinick, & Cohen, 1999; Etkin, Egner, & Kalisch, 2011) and fear extinction (Milad, Wright, et al., 2007; Northoff et al., 2006), all processes known to be affected in PTSD (American Psychiatric Association, 2013).

The hippocampus is a key region in learning and memory (Eichenbaum, 2004; Squire, 1992; Squire et al., 2004) and also plays a role in the regulation of the stress response

(Jacobson & Sapolsky, 1991). Alterations in the hippocampus are implicated in the etiology of PTSD (Bremner, 2001; Gilbertson et al., 2002; Sapolsky, 2000a). Hippocampal volume has been shown to affect contextual fear conditioning in humans (Pohlack et al., 2012), and smaller hippocampal volume has been associated with increased risk (Gilbertson et al., 2002), longer duration of illness (Apfel et al., 2011; Chao, Yaffe, Samuelson, & Neylan, 2014), and poorer treatment response (Rubin et al., 2016; van Rooij et al., 2015) in PTSD.

The medial prefrontal cortex is involved in multiple processes relevant to PTSD. The vmPFC and ACC have been implicated in affective and cognitive processing respectively, including the regulation of fear expression, memory, and emotional processing (Diekhof, Geier, Falkai, & Gruber, 2011; Etkin et al., 2011; Milad, Quirk, et al., 2007; Milad, Wright, et al., 2007; Northoff et al., 2006). Structural reductions in these two related but functionally distinct regions could explain the dual psychopathologies observed in PTSD: affective symptoms such as hyperarousal and numbing (American Psychiatric Association, 2000; Ehlers & Clark, 2000) as well as cognitive symptoms including memory deficits (Bremner, Scott, Delaney, & Southwick, 1993; Vasterling, Brailey, Constans, & Sutker, 1998) and failure to learn fear extinction (Milad et al., 2009; Milad, Wright, et al., 2007). Regions within the medial prefrontal cortex also show strong connections to the limbic system, including the amygdala (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995), and connectivity between these regions has been shown to be reduced in PTSD (Cisler, Steele, Smitherman, Lenow, & Kilts, 2013).

There is also evidence that the hippocampus and the medial prefrontal cortex may be particularly vulnerable to stress, as these regions show high structural and functional plasticity throughout the lifespan (Altman, 1962; Gould et al., 1999; McEwen & Morrison, 2013; Wenger & Lövdén, 2016). The hippocampus, along with the olfactory bulb, is the only site of neurogenesis in the adult human brain, and chronic stress is known to reduce dendritic arborization and neurogenesis in the hippocampus (Reagan & McEwen, 1997; Sapolsky et al.,

1990). The medial prefrontal cortex is one of the last regions to mature (Giedd & Rapoport, 2010; Gogtay et al., 2004) and one of the first to show age-related decline (Raz et al., 2005; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) and there is evidence that stress accelerates the aging process (Kerr, Campbell, Applegate, Brodish, & Landfield, 1991; Sapolsky, 1992; Sapolsky, Krey, & McEwen, 1986). In addition, both the hippocampus and medial prefrontal cortex are rich in glucocorticoid receptors, making them particularly susceptible to the effects of chronic stress (McEwen & Morrison, 2013; McEwen & Sapolsky, 1995; Sapolsky, 2000b), while increased glucocorticoid sensitivity has been observed in PTSD populations (Steudte-Schmiedgen et al., 2015; van Zuiden et al., 2012).

There is a conflict in the literature regarding alterations in amygdala volume in PTSD, and this is further complicated by conflicting results regarding the impact of stress on amygdala volume. Work in animals has generally demonstrated an increase in amygdala volume in response to chronic stress (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Mitra & Sapolsky, 2008; Vyas, Mitra, Rao, & Chattarji, 2002; Vyas, Pillai, & Chattarji, 2004). However, in humans some studies have found that stress correlates with increased amygdala volume (Mehta et al., 2009), while others show that stress correlates with reduced amygdala volume (Edmiston et al., 2011; Hanson et al., 2015), or has no effect (Andersen et al., 2008). One meta-analysis of adults and children with PTSD found significantly smaller amygdala volume (Karl et al., 2006), while another meta-analysis of adults only found no significant difference between PTSD patients and controls (Woon & Hedges, 2009).

At a functional level, PTSD is associated with hyper-responsivity of the amygdala and hypo-responsivity of the hippocampus and vmPFC when confronted with threatening or fear-inducing stimuli (Hughes & Shin, 2011; Shin, Rauch, & Pitman, 2006). A neurocircuitry model of PTSD proposes that there is a failure to inhibit a fear reaction in response to threat, through reduced top-down and bottom-up control of the amygdala by the vmPFC and hippocampus respectively (Rauch, Shin, & Phelps, 2006). PTSD patients have previously

demonstrated less prefrontal neural activity than controls in response to threat-related stimuli (Rauch et al., 2006; Shin et al., 2006) and during down-regulation of negative emotion (New et al., 2009; Rabinak et al., 2014; Xiong et al., 2013).

As previously discussed, PTSD is associated with greater spontaneous use of suppression to down-regulate negative emotion (Shepherd & Wild, 2014) and shifting from suppression to reappraisal is associated with reductions in symptoms (Boden et al., 2013; Price et al., 2006). Cognitive reappraisal and expressive suppression have been shown to be both functionally and temporally distinct. Previous work in healthy individuals (Goldin, McRae, Ramel, & Gross, 2008) has demonstrated that during emotion regulation, patterns of neural activity differ between reappraisal and suppression and change over time, with reappraisal showing a pattern of high initial medial prefrontal neural activity that then decreases over time, and suppression showing low initial medial prefrontal neural activity that then increases. Goldin and colleagues conclude that the early activation of prefrontal control regions during reappraisal leads to the effective down-regulation of amygdala reactivity, accompanied by successful regulation of the emotional response and a reduced need for continued cognitive control. Conversely, during suppression, later activation of prefrontal control regions seemingly fails to inhibit the emotional response, leading to a need for sustained activity in these regions and no decrease in amygdala activity. However, no PTSD neuroimaging work to date has contrasted different emotion regulation strategies, or examined how neural activity may change over time. It is therefore unclear whether and how neural activity alters during an unfolding emotional response in PTSD, and whether patterns of change differ between patients and controls. Based on neuroimaging work in PTSD, one may expect that prefrontal neural activity will be lower in PTSD patients than controls during all stages and for all forms of emotion regulation (New et al., 2009; Rabinak et al., 2014; Rauch et al., 2006; Xiong et al., 2013). Alternatively, if PTSD is particularly associated with the use of suppression (Shepherd & Wild, 2014), then one may expect that PTSD patients instructed

to use reappraisal will rather demonstrate a pattern similar to suppression in healthy controls, with lower initial prefrontal neural activity, which then increases over time (Goldin et al., 2008). Further work is required to more thoroughly investigate how neural activity during down-regulation of negative emotion may vary depending on the type of emotion regulation strategy being implemented and where along the timeline this is assessed.

Validity of a clinical diagnosis in neuroimaging research

Much recent work has focused on biological correlates of the complex clinical construct that is PTSD. For example, as outlined above, meta-analyses of structural neuroimaging studies of PTSD reveal smaller gray matter volumes in the hippocampus and prefrontal cortex (Karl et al., 2006; Kitayama et al., 2005; Kühn & Gallinat, 2013). However, results from individual studies have been inconsistent or contradictory. One potential reason underlying inconsistencies or failures of replication in the literature may be unknown rates of malingering – symptom exaggeration or simulation – within PTSD populations. PTSD is particularly vulnerable to malingering due to the subjective nature of the symptoms reported and because diagnosis is often associated with reinforcing gains, such as financial compensation and avoidance of hazardous work assignments, particularly in military populations.

This is highly problematic both when searching for neurobiological markers for PTSD and when assessing therapeutic improvements. For example, many studies seek to distinguish the neural correlates of PTSD, separate from stress exposure through the use of stress-exposed healthy controls (Kühn & Gallinat, 2013). However, if the PTSD populations being assessed also contain malingerers, essentially stress-exposed but healthy individuals, this would significantly reduce the ability to reliably and robustly detect differences between these groups.

In addition, there is a lack of consistent treatment efficacy effects in PTSD, with a large number of PTSD patients reporting that they do not recover (Bisson et al., 2013;

Bradley et al., 2005; Kessler, 1995; Schottenbauer et al., 2008). Part of this lack of treatment efficacy can be attributed to individuals over-reporting symptoms and failing to acknowledge or report therapeutic gains. Indeed, it has previously been recommended that SVTs be included in studies of PTSD, that results from military and civilian populations be reported separately, and that patients currently receiving or awaiting financial benefits based on a continued diagnosis of PTSD be excluded from clinical trials (Charney et al., 1998; Freeman, Powell, & Kimbrell, 2008).

In PTSD neuroimaging research, a clinical diagnosis is often taken at face validity. For example, in a recent meta-analysis of PTSD neuroimaging studies, none of the nine studies included reported the use of SVTs to confirm diagnosis (Kühn & Gallinat, 2013). However, the practical implications of failing to distinguish credible patients from malingerers on experimental results remain unclear. Specifically, by including malingerers – trauma-exposed individuals without PTSD – in the patient group, studies contrasting trauma-exposed individuals with and without PTSD (Kühn & Gallinat, 2013) necessarily have a reduced ability to observe reliable differences between these groups. Another possibility is that malingerers may be distinct from trauma-exposed individuals both with and without PTSD. In order to successfully deceive clinicians and receive a PTSD diagnosis, malingerers must continually and convincingly present a falsified clinical profile and inhibit their true behavioral and psychological responses. Malingerers may thus show differences in regions related to response inhibition or deception. In this instance, the inclusion of malingerers may lead to findings that are inconsistent with the broader literature, reflecting malingering-specific effects. If differences between malingerers and credible PTSD patients can be observed, particularly in regions implicated in PTSD or deception, it would serve as strong evidence that SVTs should be routinely incorporated into studies of PTSD to ensure the validity of the clinical populations and the robustness and reproducibility of findings. This

may also aid in the re-interpretation of previous findings that are anomalous or inconsistent with the broader literature.

2.4. Stress in Specific Populations

Stress and the military

Practical and ethical considerations necessarily impact the level and types of stressors that can be investigated in experimental settings with humans. In contrast to animal work, the intensity and duration of the stressors investigated experimentally in humans are much lower. As such, the stress response and its long-term physical and mental effects are much mitigated or reduced, with a corresponding reduction in the ability to meaningfully detect and delineate the neural effects. One way to overcome this limitation is to investigate settings in which humans are exposed to extreme stress or trauma as part of their daily lives.

This dissertation will focus specifically on violent stress, mainly in military populations. Military deployment and combat exposure are specific and highly relevant forms of extreme stress and trauma, and research into how combat exposure and combat-related PTSD may affect the brain has strong real-world implications. Increases in conflict across the globe in recent years have led to a rise in the number of individuals exposed to combat stress and war-related trauma, with a corresponding increase in the prevalence of stress-related disorders, and PTSD remains a current and significant issue for military populations today. In addition, PTSD owes its conceptual background to research in military populations, with formal identification of PTSD as a clinical diagnosis arising from research in traumatized military populations.

Violence and combat exposure provide a strong model when investigating the effects of stress on the brain. Psychological research on stress has usefully identified and investigated many events as potential stressors. However, the same event may be interpreted differently depending on the individual and the environment, and certain events may or may not be

perceived as stressful depending on the context and the individual's personality. As an illustrative example, in the highly influential Social Readjustment Rating Scale (Holmes & Rahe, 1967), the authors include Christmas as one of the 43 stressful life events that can cause illness, and give Christmas a single numeric value representing its impact on health. However, no weight is given to how stressful the individual perceived the event to be, although from one's own experience one knows that Christmas may be less or more stressful for certain individuals, or for the same individual in different situations. Conversely, in the Perceived Stress Scale (Cohen, 1994), no specific events are listed. Rather, the individual is asked to rate how often they experienced thoughts or feelings of stress in the last month. On this scale, individuals may report the same level of stress and receive the same score based on wildly different numbers and intensities of stressors. In both these cases, research into the effects of stress on the brain, behavior and cognition may be limited by considerations on how to measure stress, and how to weigh objective and subjective appraisals of stressful events. One possibility to overcome this issue is to focus on stressors that are likely to elicit a strong stress response across individuals and environments, with effects less likely to be moderated or mitigated by factors of personality and context. For example, unlike certain perceived psychosocial stressors, violence and war are likely to consistently elicit a strong stress response in all exposed individuals.

One potential limitation regarding the use of specific populations, such as the military, is the generalizability of results to other populations. Although the stress response is broadly similar across both scenarios and species, further work is also required to directly test whether results from military populations replicate in civilian populations. In my work, I will mainly focus on adult male military populations. However, I will also explore how results from this population (*Paper I*) may replicate in an adolescent, mixed-gender civilian population (*Paper II)*.

3. Aims of Dissertation

Given the theoretical and empirical foundations described in the previous sections, I seek to achieve the following goals in my dissertation:

1. Neuroimaging research on stress in adults has mainly focused on PTSD, with subclinical trauma-exposed individuals often serving as controls. I aim to investigate the neural correlates of stress exposure in subclinical populations, to assess how stress relates to gray matter volume in individuals without a clinical diagnosis of PTSD, with implications for the current dichotomy between clinical and subclinical populations in stress research.
2. The factors that determine whether an individual will recover or develop persistent and debilitating symptoms following trauma exposure remain unclear. I explore potential psychological and neural factors that may underlie the development and maintenance of symptoms, with implications for our understanding of the etiology and treatment of PTSD.
3. The hippocampus is hypothesized to play a key role in PTSD symptomatology. I will investigate whether hippocampal volume increases following therapeutic interventions for PTSD, thereby demonstrating recovery-related hippocampal gain in combat PTSD for the first time, with implications for our understanding of the neural mechanisms underlying treatment of PTSD. In addition, I will investigate the utility of video gaming as a novel intervention for PTSD, at the neural and behavioral levels.
4. The use of SVTs is now recommended to ensure the validity of a PTSD diagnosis. However, in PTSD neuroimaging research, diagnoses are often taken at face validity. I aim to provide first evidence of the neural correlates of symptom exaggeration in PTSD, with implications for the incorporation of SVTs into future studies of PTSD.

4. Summary of Papers

4.1. Paper I

Butler, O., Adolf, J., Gleich, T., Willmund, G., Zimmermann, P., Lindenberger, U., Gallinat, J., Kühn, S. (2017). Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population. *Translational Psychiatry*, doi: 10.1038/tp.2016.288

In this paper, we investigated the effects of long-term stress exposure on the brain in a sub-clinical population, and how stress-related differences in brain volume relate to psychological symptoms. Specifically, we assessed individuals with combat-related trauma exposure and correlated duration of military deployment with gray matter volume.

Theoretical background

Neuroimaging research on stress exposure in adult human populations has mainly focused on PTSD. However, only a small minority of individuals exposed to trauma will go on to develop PTSD. To date, the neural correlates of stress exposure in individuals who do not meet the criteria for PTSD have generally been overlooked. Rather, trauma-exposed individuals without a clinical diagnosis have often served as a control group when investigating PTSD. However, this assumes a dichotomy between clinical and subclinical populations that may not be supported at either psychological and neural levels. To investigate this, we correlated duration of military deployment with gray matter volume in combat-exposed individuals without a clinical diagnosis. Military deployment is a specific instantiation of chronic stress, and has many elements that may be stressful. In addition to acute, violent stressors such as engaging in combat, there is also growing recognition of "wear and tear" as a source of stress injury. Elements of military deployment relating to wear and tear include separation from family and loved ones, changes to sleeping and eating patterns,

limited opportunity for rest, and moral conflict between the ethical views of the individual and the reality of combat environments. In addition, military deployment is an objective and verifiable measure that is directly comparable across individuals. As such, military deployment provides a strong measure of stress exposure, both theoretically and practically. We hypothesized that duration of military deployment would correlate with reductions in brain regions previously implicated in PTSD, and that gray matter reductions would correlate with increased psychological symptoms.

Methods

Twenty-seven male soldiers (aged 23 – 42) who had experienced combat-related trauma and were free of psychiatric disorders were recruited from the German Federal Armed Forces. Participants completed structural MRI neuroimaging and psychological questionnaires assessing PTSD symptoms and general psychological distress. Whole-brain analysis was performed using voxel based morphometry (VBM) to investigate the correlation between duration of military deployment and gray matter volume. Gray matter values from the clusters identified in the whole-brain analysis were then extracted. To assess the relationship between military deployment, gray matter volume and psychological symptoms, correlations were calculated between days of deployment, deployment-related gray matter volume and psychological symptoms.

Major findings

Duration of military deployment correlated with smaller gray matter volume in the ACC and vmPFC, regions involved in emotion regulation and fear extinction that have previously been shown to be reduced in PTSD population and the clusters identified in the current analysis directly overlapped with regions previously observed in a meta-analysis of PTSD neuroimaging studies (Kühn & Gallinat, 2013). In addition, deployment-related reductions in gray matter, but not duration of military deployment, negatively correlated with psychological symptoms.

The current findings have two major implications. First, smaller prefrontal gray matter volume is likely to represent a consequence of stress exposure, rather than a pre-existing risk factor for PTSD. Second, subclinical populations display reduced gray matter volumes in regions previously implicated in PTSD, and reductions in these regions correlate with increases in psychological symptoms. As such, the current dichotomy between clinical and subclinical populations does not appear to be supported at either the psychological or neural level. Rather, stress-related psychological symptoms and stress-related brain changes may be more meaningfully investigated at a continuous level.

4.2. Paper II

Butler, O., Yang, X. F., Laube, C., Kühn, S., Immordino-Yang, M. H. (2018). Community Violence Exposure Correlates with Smaller Gray Matter Volume and Lower IQ in Urban Adolescents. *Human Brain Mapping*, doi: 10.1002/hbm.23988

In this paper, we sought to replicate the findings of *Paper I* in an independent sample by correlating stress exposure, in this case community violence, with gray matter volume in an urban adolescent population using the same approach as in *Paper I*.

Theoretical background

Adolescence is a key neurodevelopmental period, during which time an individual may be more susceptible to the effects of stress and other environmental insults. Community violence exposure is a significant public health issue for urban adolescents and is associated with poorer cognitive, emotional, and psychological outcomes. However, to date no study has investigated the neural correlates of community violence exposure in adolescents. We hypothesized that exposure to community violence would correlate with smaller gray matter volume in those prefrontal regions identified in *Paper I*.

Methods

Sixty-five healthy, non-delinquent adolescents (aged 14–18, 55% female) were recruited from moderate to high-crime urban neighborhoods. Participants completed structural neuroimaging and cognitive assessment. Whole-brain analysis was performed using VBM, to investigate the relationship between community violence exposure and gray matter volume. In addition, community violence exposure was correlated with IQ.

Major findings

Community violence exposure negatively correlated with gray matter volume in the ACC, vmPFC, and IFG, regions involved in high-level cognitive functions and previously shown to be reduced in PTSD and combat-exposed military populations. In addition, community

violence exposure also correlated with lower IQ. These results provide a replication of the findings of *Paper I*, in which stress exposure correlates with smaller brain volume in prefrontal regions in a subclinical population. In addition, these results provide first evidence of the neural underpinnings of previously observed psychological and cognitive effects of community violence on adolescents.

4.3. Paper III

Butler, O., Willmund, G. , Gleich, T., Zimmermann, P., Lindenberger, U., Gallinat, J., Kühn, S. (2018). Cognitive reappraisal and expressive suppression of negative emotion in combat-related posttraumatic stress disorder: A functional MRI study. *Cognitive Therapy and Research,* doi: 10.1007/s10608-018-9905-x

In *Paper I* and *Paper II*, we demonstrated that smaller prefrontal gray matter volume, typically associated with PTSD populations, can also be observed in subclinical populations, and may represent a more general effect of stress exposure rather than a specific risk factor for PTSD. Nevertheless, some functional and neural factors may distinguish individuals with and without PTSD, and help explain why some individuals recover following trauma exposure, while others experience persistence or worsening of symptoms. One potential reason symptoms fail to resolve is the use of maladaptive emotion regulation strategies when faced with negative emotions. Therefore, we turned to potential functional differences between PTSD patients and trauma-exposed individuals without PTSD. In this study, we used fMRI to compare two emotion regulation strategies, cognitive reappraisal and expressive suppression, in combat-related PTSD.

Theoretical background

Psychological symptoms are common in the aftermath of a traumatic event, and in the majority of cases will resolve in the first few weeks following trauma exposure. However, a significant minority of individuals will go on to develop the persistent and debilitating symptoms that characterize PTSD. It has been hypothesized that the use of maladaptive emotion regulation strategies when faced with negative emotions may underlie the failure of some individuals to recover from typical short-term post-traumatic psychological distress. A process model of emotion regulation distinguishes between early, antecedent-focused emotion

regulation strategies such as cognitive reappraisal, and later, response-focused strategies such as expressive suppression.

Previous work in healthy individuals has demonstrated that, at a neural level, cognitive reappraisal is characterized by a pattern of high preparatory neural activity to successfully prevent an emotional response from occurring, which then decreases over time as it is no longer required. In contrast, suppression is characterized by a pattern of low initial prefrontal neural activity that then increases over time, as an individual recruits more cognitive resources to attempt to suppress a burgeoning emotional response.

Results from previous neuroimaging studies in PTSD suggest that PTSD patients display lower prefrontal neural activity compared with controls during emotion regulation. However, no study to date has compared different emotion regulation strategies, or distinguished between task preparation and image presentation.

We aim to investigate the neural dynamics of emotion regulation in PTSD, and to clarify whether during cognitive reappraisal, individuals with PTSD display lower prefrontal neural activity during both task preparation and image presentation, or a pattern of low preparatory activity followed by higher sustained activity, similar to the pattern previously observed in suppression in healthy controls.

Methods

Eighteen male soldiers with combat-related PTSD prior to onset of therapy and 27 combat-exposed male soldiers free of psychiatric disorders completed an fMRI emotional regulation task. During the task, individuals were presented with combat-related images in an MRI scanner. Prior to each image, individuals were instructed to either feel, reappraise, or suppress their emotional response. Neural activity for task preparation and image presentation were analyzed separately.

Major findings

In the reappraise condition, the PTSD group showed lower neural activity than the control group in medial prefrontal areas during task preparation, and higher activity than controls during image presentation. No differences in neural activity were observed between the groups in the feel or suppress conditions during task preparation or image presentation. The pattern of neural activity observed in the PTSD group during reappraisal is similar to that previously observed in expressive suppression in healthy controls. These findings suggest that even when instructed to cognitively reappraise, PTSD patients may instead employ expressive suppression to regulate negative emotion.

4.4. Paper IV

Butler, O., Willmund, G., Gleich, T., Gallinat, J., Kühn, S., Zimmermann, P. (2018). Hippocampal gray matter increases following psychological treatment for combat-related posttraumatic stress disorder. *Brain and Behaviour*, doi: 10.1002/brb3.956

In this paper, we conducted a pilot longitudinal study to investigate structural changes in PTSD following psychotherapy. Individuals with combat-related PTSD were recruited prior to therapy and randomly assigned to either a therapy group or a waiting-list control group. Hippocampal and amygdala gray matter volume were assessed using a region of interest (ROI) approach, once prior to therapy and once following therapy.

Theoretical background

Smaller hippocampal volumes are one of the most consistent findings in adult PTSD populations (Karl et al., 2006; Kitayama et al., 2005; Kühn & Gallinat, 2013) and have been linked to longer duration and poorer response to therapy in PTSD. Psychotherapy is one of the most common and effective therapeutic interventions available for PTSD (Foa et al., 2000), and increases in hippocampal volume are linked to improvements in cognition and reductions of symptoms in PTSD (Levy-Gigi et al., 2013; Vermetten et al., 2003). However, to our knowledge only two studies to date have assessed changes in gray matter prior to and following psychotherapy using a waiting-list control group (Boukezzi et al., 2017; Lindauer et al., 2005), and no work has demonstrated an increase in hippocampal volume in medication-free PTSD patients following psychotherapy. We conducted a pilot longitudinal study to explore changes in hippocampal gray matter volume in medication-free PTSD patients following psychotherapy. We hypothesized that the therapy group would show increases in hippocampal gray matter volume, compared to the control group.

Methods

Fifteen male soldiers with combat-related PTSD completed structural MRI neuroimaging at two time points. All participants were free of medication, recruited prior to therapy, and randomly assigned to either a therapy group or a waiting-list control group. Neuroimaging data was available for six individuals in the therapy group and nine individuals in the waiting-list control group at both assessments. Bilateral anatomical hippocampal and amygdala gray matter volumes were calculated using a ROI approach. Repeated measures analysis of variance (ANOVA) was conducted to assess change in hippocampal and amygdala volume.

Major findings

There was a significant group-by-time interaction for the hippocampus, with increases in hippocampal volume in the therapy group, and a similar statistical trend was observed in the amygdala. We find first evidence of an increase in hippocampal volume in PTSD following psychotherapy in medication-free individuals. Previous work with a similar design failed to observe an increase in hippocampal volume following psychotherapy (Boukezzi et al., 2017; Lindauer et al., 2005). One potential reason for the disparity between the current and previous results is that the current sample of young adult males represents a more homogeneous group than the samples analyzed by Lindauer and colleagues and Boukezzi and colleagues, in which approximately half of the participants were female and the mean age was higher. Age and gender are known to play a role in hippocampal neuroplasticity, thus, the use of a younger, male population may provide a greater ability to detect small effects.

4.5. Paper V

Butler, O., Herr, K., Willmund, G., Gallinat, J., Kühn, S., Zimmermann, P. (under review). Trauma, Treatment and Tetris: Video gaming increases hippocampal volume in combat-related posttraumatic stress disorder.

Following on from the proof-of-concept pilot study presented in *Paper IV*, we now turn to investigating a potential adjunct to traditional psychotherapy, in the form of the video game Tetris. We built upon previous work on Tetris as an intervention to reduce intrusive memories following trauma (Holmes et al., 2009; Horsch et al., 2017), and extended it by trialing a Tetris intervention in individuals with current combat-related PTSD undergoing psychotherapy. In a similar approach to *Paper IV,* individuals with combat-related PTSD were recruited prior to onset of therapy and randomly assigned to either a combination psychotherapy and Tetris group or to a therapy-only control group. Again, we assessed participants prior to and following therapy and compared gray matter volume changes using both whole-brain and ROI approaches.

Theoretical background

PTSD is characterized by recurrent, vivid intrusive memories of traumatic events, causing distress and functional impairment for affected individuals. Remembering is an active process, and for a period following reactivation a memory trace remains in a labile state as it is reconsolidated back into long-term memory. During this reconsolidation period, the memory trace is susceptible to interference, and completing a demanding but unrelated task can weaken reconsolidation and reduce subsequent retrievals. Recent work has provided initial evidence of the utility of Tetris as an intervention to reduce the occurrence of intrusive memories following trauma (Holmes et al., 2009; Horsch et al., 2017; Iyadurai et al., 2017). However, no study to date has investigated Tetris as a method for weakening traumatic memories, and therewith psychological distress, in individuals with current PTSD. In

addition, video gaming and spatial memory training has been shown to produce increases in hippocampal volume (Kühn et al., 2014; Woollett & Maguire, 2011) and increases in hippocampal volume are linked to improvements in cognition and reductions in symptoms in PTSD (Levy-Gigi et al., 2013; Vermetten et al., 2003). Tetris therefore provides a promising potential therapeutic intervention, acting at both the psychological and neural levels. We hypothesized that playing Tetris would correlate with increases in hippocampal volume and decreases in psychological symptoms compared to psychotherapy alone.

Methods

Forty male soldiers with current combat-related PTSD were recruited prior to onset of therapy. Participants were randomly allocated to a Tetris group or an active control group. Individuals in the control group completed EMDR psychotherapy as usual, while individuals in the Tetris group also played 60 minutes of Tetris per day in addition to EMDR. Participants were assessed with structural MRI neuroimaging and psychological questionnaires prior to and following therapy. Whole-brain analysis was conducted using VBM to assess changes in gray matter volume in the Tetris group following therapy compared to the control group. Correlations between change in hippocampal volume following therapy were correlated with changes in psychiatric symptoms between completion of therapy and follow-up, approximately six months later. Increases in hippocampal volume correlated with decreases in psychiatric symptoms in the Tetris group but not the control group.

Major findings

The Tetris group showed increases in hippocampal gray matter volume following completion of therapy compared to the therapy-only control group. Psychological symptoms were reduced following therapy across all participants, and both groups continued to show significant reductions in PTSD symptoms at six-month follow-up assessment. However, only the Tetris group continued to show significant reductions in anxiety and depression symptoms from pre-therapy levels at follow-up. In addition, increases in hippocampal volume following

therapy correlated with further decreases in psychological symptoms at follow-up in the Tetris group but not the control group. The key finding of this study is that Tetris may be useful as an adjunct therapeutic intervention for PTSD, increasing hippocampal volume and leading to wider retention of therapy-related gains. This study provides first evidence of the utility of a Tetris video-gaming intervention in individuals with current PTSD.

4.6. Paper VI

Butler, O., Herr, K., Willmund, G., Gallinat, J., Zimmermann, P., Kühn, S. (under review). Neural correlates of malingering: Larger hippocampal volume correlates with symptom aggravation in combat-related posttraumatic stress disorder.

In *Paper VI*, we pooled data from *Paper IV* and *Paper V* to investigate the neural correlates of symptom aggravation in PTSD. PTSD patients were identified as either credible or as malingerers using the Morel Emotional Numbing Task (MENT). The structural differences between these groups were explored using whole-brain and ROI analysis.

Theoretical background

Since its formulation, diagnosis of PTSD has increased to the point where it is now the third most commonly used diagnosis by psychologists (Evans et al., 2013). This increase is due, in part, to increasing awareness of the condition and reductions in stigma attached to a diagnosis, leading to more individuals seeking a diagnosis following trauma exposure. However, a diagnosis of PTSD can be accompanied by gains such as financial compensation or avoidance of hazardous work assignments, meaning that some individuals may be incentivized to aggravate or exaggerate their symptoms to meet the diagnostic criteria. PTSD is vulnerable to such aggravation as diagnosis is based on the individual's self-reported level of symptoms and functional impairment, and no definitive diagnostic test for PTSD exists.

The use of SVTs to validate a diagnosis and to identify individuals showing signs of symptom aggravation is now recommended for PTSD. However, these are not commonly used, particularly in research, and in the vast majority of neuroimaging studies of PTSD diagnosis is taken at face validity. This is highly problematic when investigating neurobiological correlates of PTSD, as results may be biased by an unknown portion of malingerers in PTSD populations. However, how malingerers may bias results remains

unclear as no previous neuroimaging study has compared credible PTSD patients to malingerers.

Methods

By pooling data from previous work, we identified a sufficient number of potential malingerers to warrant a comparison of credible PTSD patients and malingerers. We distinguished between credible PTSD patients and malingerers using the MENT (Morel, 1998), a two-alternative forced choice test to detect response bias in PTSD (Morel, 1998) that has been shown to have high sensitivity and specificity in detecting symptom exaggeration (Morel, 1998, 2013). From a sample of male PTSD patients recruited prior to onset of therapy, 37 were identified as credible and nine were identified as malingerers. We conducted whole-brain and ROI analysis to assess differences in gray matter volume between groups.

Major findings

Malingerers displayed larger gray matter volumes than credible patients, in the thalamus and IFG at the whole-brain level, and in the hippocampus at the whole-brain and ROI levels. Notably, the hippocampus is traditionally found to be reduced in PTSD patients and, as previously discussed, may represent a PTSD-specific result, rather than relating to stress exposure in general. The thalamus and inferior frontal gyrus (IFG) are both implicated in deception, while the IFG is known to play a role in inhibition. These differences may exist prior to malingering; for example, larger volumes in the thalamus and IFG may allow individuals to successfully deceive clinicians. Alternatively, these may develop as a result of malingering, for example, continuously presenting an exaggerated symptom profile and inhibiting responses that may reveal their true clinical presentation may lead to increases in gray matter volume.

These findings provide first evidence of the neural correlates of malingering in PTSD. Demonstrable differences can be observed between credible patients and malingerers in regions involved in PTSD, inhibition, and deception. The results emphasize that SVTs should

be routinely incorporated into neuroimaging studies specifically, and into PTSD research more broadly, to ensure the credibility of the populations under observation and the robustness of results.

5. Discussion

In the following section, I will summarize and evaluate the major findings of my research and detail how these findings contribute to the field of stress-related neuroimaging. I will consider some of the limitations, outline some of the open questions thereby providing potential directions for future work, and finally draw some general conclusions

5.1. Summary and Evaluation of Major Findings

Subclinical populations demonstrate stress-related reductions in prefrontal gray matter volume

Subclinical populations are largely overlooked in neuroimaging stress literature. Previous work has generally treated trauma-exposed individuals without a clinical diagnosis as a single, homogenous "healthy" population, with little if any work attempting to quantify the amount of stress these individuals have experienced, or seeking to correlate stress exposure with psychological or neural effects. However, the results of *Paper I* and *Paper II* call for a more nuanced approach when investigating the relationship between stress and gray matter volume. By employing continuous rather than absolute measures of stress, we demonstrate in *Paper I* and *Paper II* that meaningful effects of stress on the brain, cognition, and mental health can also be observed in individuals who do not meet the criteria for a clinical diagnosis. This has important implications for future research, as the current dichotomy between clinical and subclinical populations does not appear to be supported at the neural, cognitive or psychological levels. Rather than treating trauma-exposed subclinical individuals as a homogenous, healthy control group, these individuals instead may provide a useful and hitherto under-utilized population when investigating stress and the brain. This also has practical benefits, as it is easier to recruit and test individuals who are not suffering from persistent and debilitating psychiatric symptoms. This is particularly relevant for studies using MRI neuroimaging, as panic attacks and claustrophobia can prevent individuals with PTSD

from participating. In addition, the majority of individuals exposed to trauma do not go on to develop PTSD, and subclinical populations are more representative of trauma-exposed populations in the real world. As such, investigating trauma-exposed individuals without a clinical diagnosis will also improve the generalizability of neuroimaging stress research.

Stress exposure correlated with smaller prefrontal gray matter volumes in regions traditionally found to be reduced in PTSD populations, specifically the vmPFC and ACC were found to be affected. These regions are involved in the regulation of affect, cognition, and the expression and extinction of fear, and are also proposed to play a key role in the neurocircuitry of PTSD. Although the precise clinical significance of these prefrontal reductions is difficult to interpret, particularly given the cross-sectional nature of the data, one possibility is that stressful events act as neurological insults that gradually reduce the individual's ability to cope with subsequent stressful events, increasing psychological symptoms and reducing resilience. It is possible that individuals demonstrating stress-related reductions in gray matter volume may be particularly vulnerable to PTSD, if exposed to additional stress. This is in line with previous work that has demonstrated a dose–response relationship between stress and PTSD, with higher rates of trauma exposure correlating with increased incidence of PTSD (Neuner et al., 2004). If individuals with stress-related reductions in prefrontal gray matter volume are indeed shown to be at increased risk, this would have important implications for the prevention of PTSD. In the future, MRI could be used to screen high-risk populations, such as the military, or first responders, and individuals identified as highly susceptible could receive greater levels of training and support.

When reviewing the results of *Paper I* and *Paper II* and the relationship between stress exposure and gray matter volume in subclinical populations, one should also note "the dog that didn't bark". No correlation between stress exposure and hippocampal volume was observed in either *Paper I* or *Paper II*, even when adapting a more lenient threshold or a smaller smoothing kernel. As such, smaller prefrontal volumes may represent a more general

effect of stress exposure, while smaller hippocampal volumes may relate to PTSD specifically. Although it is difficult to interpret a null-finding, this is in line with previous work (Gilbertson, 2002, Kasai, 2008) and also fits with our other findings. In *Paper IV* and *Paper V*, hippocampal volume, but not prefrontal gray matter volume, was shown to increase following therapeutic interventions for PTSD, and increases in hippocampal volume during therapy correlated with further reductions in psychological symptoms following discharge. In *Paper VI*, patients diagnosed with combat-related PTSD were classified as either credible or malingering, based on their performance on a SVT. Credible PTSD patients showed smaller hippocampal volumes than malingerers, but no difference between the groups was observed in the vmPFC or ACC. One should note that all individuals had been exposed to combat-related trauma, and the number and duration of military deployments did not differ between the groups. This again supports the theory that smaller hippocampal volumes may relate to PTSD specifically. This has important implications both for the interpretation of previous work and for the design of future studies. For example, in a previous meta-analysis of neuroimaging studies comparing PTSD patients and trauma-exposed individuals without PTSD, PTSD was found to correlate with reductions in the hippocampus, ACC, vmPFC and the middle temporal gyrus (Kühn & Gallinat, 2013). Although the studies included in the meta-analysis matched participants for type of trauma, e.g. motor vehicle accidents, fires, subway accident, none of the studies assessed stress on a continuous level. It is therefore possible that individuals in the PTSD group experienced a greater number or severity of stressful events, and smaller prefrontal gray matter volumes reflect higher levels of stress exposure rather than a PTSD specific effect. Although this cannot be tested retrospectively, it can inform future work. Studies attempting to distinguish PTSD specific effects from those of stress and trauma exposure, may seek to assess and control for stress in a continuous manner, when comparing PTSD patients and trauma exposed individuals without PTSD.

The neural processes underlying emotion regulation are altered in PTSD

Throughout our lives, many of us will experience traumatic events, and trauma-related symptoms are common in the period immediately following trauma exposure. For the majority, these symptoms resolve in the first month following exposure, but a subset of individuals will go on to develop the persistent symptoms that characterize PTSD. When assessing factors that may distinguish individuals with PTSD from trauma-exposed controls, in addition to smaller hippocampal volumes, one may also consider functional and behavioral factors. One reason for the failure of symptoms to resolve over time may be the use of emotion regulation strategies that aim to suppress rather than modify an emotional response, when confronted with negative emotions. Greater understanding of the neural mechanisms underlying different emotion regulation strategies, and how these differ between clinical and non-clinical populations, is crucial to identifying what factors underlie the development and maintenance of PTSD following traumatization.

In *Paper III*, a process model of emotion regulation was explored in PTSD using fMRI. Two emotional regulation strategies, cognitive reappraisal and expressive suppression, were compared in PTSD patients and controls. Patients with combat-related PTSD and combat-exposed individuals without mental illness completed an fMRI emotion regulation task to down-regulate negative emotion to combat-related images using either cognitive reappraisal or expressive suppression. In addition, neural activity during task preparation and stimulus presentation were analyzed separately.

Previous studies have not distinguished between these strategies or phases and show rather a general pattern of reduced neural activity in PTSD patients during emotion regulation. We found however, that during cognitive reappraisal, PTSD patients show a similar pattern of neural activity to that of expressive suppression in healthy individuals. Specifically, this is characterized by lower initial or preparatory neural activity, followed by higher neural activity during active regulation, perhaps reflecting that PTSD patients have not successfully targeted the emotional response before it occurs, and must instead continuously attempt to down-

regulate the elicited emotional response. No difference between PTSD patients and controls was observed during expressive suppression.

Paper III provides greater granularity of detail and reveals greater complexity regarding the neural dynamics of emotion regulation in PTSD than previously described. Results indicate that previous work on emotion regulation that has observed lower prefrontal neural activity may be over-simplistic. Rather, neural activity underlying emotion regulation in individuals with PTSD may vary as a function of the stage at which it is assessed, during preparation or active regulation, and the type of strategy being applied, cognitive reappraisal or expressive suppression. Based on the results of *Paper III*, I tentatively conclude that even when instructed to use cognitive reappraisal, individuals with PTSD may instead rely on expressive suppression. This is in line with previous work that demonstrated that difficulties with emotion regulation were found to be significantly associated with PTSD symptom severity and to partially mediate the relationship between PTSD and related comorbidities (Klemanski et al., 2012). Our work provides more detailed evidence of the underlying neural mechanisms and temporal dynamics of these emotion regulation difficulties, with implications for our understanding of the etiology and treatment of PTSD.

Hippocampal volumes increase following therapeutic interventions for PTSD

Smaller hippocampal volumes are one of the most consistent findings in neuroimaging studies of adult PTSD, and are linked to longer duration and poorer response to therapy. However, to our knowledge only two studies to date have assessed changes in gray matter prior to and following psychotherapy (Boukezzi et al., 2017; Lindauer et al., 2005) in medication-free individuals. In *Paper IV,* we conducted a pilot longitudinal study to explore changes in gray matter and psychological symptoms following psychotherapy. Individuals with combat-related PTSD were randomly assigned to either a therapy group or a waiting-list control group and assessed with psychological questionnaires and structural MRI at two time points. To our knowledge, *Paper IV* is the first study with this design ever conducted in combat-related

PTSD and the first to demonstrate an increase in hippocampal volume following psychotherapy in medication-free individuals. As such, *Paper IV* represents a proof-of-concept pilot study, demonstrating that changes in hippocampal volume can be observed following psychotherapy, a well-established therapeutic intervention for PTSD.

Following on from this, *Paper V* assessed a novel therapeutic intervention, building on work that has demonstrated the utility of video gaming in reducing intrusive memories following trauma, and in increasing hippocampal volume. Playing the videogame Tetris has been shown to reduce intrusive trauma-related memories in experimental and real-world settings. However, no study to date had tested Tetris in a psychiatric setting, with patients with current PTSD, and no study had assessed how playing Tetris may affect brain structure, particularly in regions related to PTSD. In *Paper V*, patients with combat-related PTSD were recruited prior to psychotherapy and randomly assigned to either a Tetris group or a therapy-only control group. Individuals in the control group completed psychotherapy as normal, while individuals in the experimental group completed a Tetris intervention in addition to therapy, playing 60 minutes of Tetris per day. Participants completed structural neuroimaging and psychological questionnaire assessments prior to and directly following therapy, approximately six weeks later. In addition, participants completed the questionnaire assessment at follow-up, approximately six-months following completion of therapy.

At the brain structural level, we observed increases in hippocampal volume in the Tetris group, at both the whole brain and ROI levels. In addition, hippocampal gray matter increases during therapy correlated with further reductions in PTSD, depression and anxiety symptoms from discharge to follow-up in the Tetris group but not the control group. We find support for the use of Tetris as an intervention for current PTSD, alongside psychotherapy. Playing Tetris may ensure that a wider range of symptom improvements are maintained following therapy, through increases in hippocampal volume.

Current interventions for PTSD have a number of limitations and there is a significant need for additional therapeutic interventions that may act as an adjunct to traditional psychotherapy for non-responders and to ensure the long-term maintenance of therapy-related gains for responders. *Paper V* provides first evidence that Tetris may be useful as an adjunct therapeutic intervention, and describes the potential underlying neural mechanisms. As such, these findings significantly advance current understanding of treatment for PTSD and have clear practical implications.

Symptom simulation correlates with larger hippocampal volumes in PTSD

The number of individuals receiving a diagnosis of PTSD has increased tremendously in recent years. This is certainly due, in part, to greater awareness of the condition and a reduction in the stigma attached to a diagnosis. However, as awareness and support increases, so too do incentives to simulate or exaggerate symptoms. PTSD is particularly vulnerable to malingering due to the subjective nature of the symptoms reported and because a diagnosis is often associated with reinforcing gains, such as financial compensation or avoidance of hazardous work assignments. Some recognition of this problem does exist, with previous work recommending that SVTs be included in studies of PTSD and individuals who receive financial benefits based on PTSD diagnosis be excluded from clinical trials. However, in the majority of PTSD neuroimaging studies, diagnosis is taken at face value and no neuroimaging study to date has distinguished malingerers from credible PTSD patients and compared these groups.

Paper VI of this dissertation assessed a population of PTSD patients, and distinguished credible patients from those showing signs of symptom exaggeration or simulation, using a SVT. Malingerers displayed larger gray matter volume than credible patients in the hippocampus, right IFG and thalamus, regions implicated in PTSD, inhibition, and deception. Our results provide first evidence of structural differences between credible PTSD patients and malingerers and emphasize the need for future neuroimaging studies to

incorporate SVTs to ensure the robustness and consistency of results. Given the novelty and relevance of these findings, as well as the clinical and scientific implications, *Paper IV* may provide a strong starting point for the timely discussion of the use of SVTs in PTSD neuroimaging, particularly in military populations.

5.2. Limitations and Future Research Directions

Sample size

In the current work sample size is a potential limitation. Small sample sizes are a common issue in neuroimaging research and low power can reduce both the ability to detect a true effect and the likelihood that a significant result reflects a true effect (Button et al., 2013; Poldrack et al., 2017). In *Paper IV*, analysis was based on 15 participants, and although the approach and sample size are comparable to previous work (Boukezzi et al., 2017; Lindauer et al., 2005), replications with larger samples are required. However, recruitment of participants to these types of studies remains a non-trivial challenge. This is perhaps reflected in the fact that, to our knowledge, *Paper IV* is the first study employing a waiting-list control group design ever conducted in combat-related PTSD. As such, balancing considerations of sufficient statistical power against the practical constraints of successfully conducting research remains a challenge. However, increasing the homogeneity of the sample under observation may increase the ability to detect effects. For example, the correlation between stress exposure and prefrontal gray matter volume observed in the more homogenous population of 27 male Caucasian soldiers in *Paper I* was replicated in the larger and more heterogeneous population of 65 male and female, Latino, East Asian, and African American adolescents in *Paper II*, giving an initial indication that results from smaller homogenous sample sizes may reliably replicate in larger heterogeneous samples.

Missing data

In *Paper IV*, five participants did not complete the second MRI assessment, while in *Paper V*, four participants did not complete the six-month follow-up assessment. Data on why individuals did not complete all assessments was not available for the current studies, as ethics prevent participants from being required to provide justification for dropping out. Based on the data that we do have, dropouts and completers showed no significant differences in age, combat experiences, duration of military deployment or scores on any of the

psychological questionnaires at initial assessment. As will be discussed below, factors like motivation and satisfaction with therapeutic interventions may also play a role in non-completion. Future studies may seek to follow up with dropouts to clarify reasons for non-completion, although ethical considerations must be balanced with a desire to capture selection effects.

Neuroimaging confounds and measurement error

Analysis of neuroimaging data using automated software packages includes multiple steps of preprocessing and processing to allow meaningful comparison across subjects, which may increase bias or error. In this dissertation, I used statistical parameter mapping (SPM), and the VBM and computational anatomy toolbox (CAT) toolboxes. The use of automated processing packages presents a significant practical advantage over manual tracing methods as it is much faster and allows for the unbiased and unconstrained analysis of whole-brain anatomy, rather than restricting analysis to distinct anatomical regions of interest. Whole-brain analysis was conducted in Paper I, Paper II, Paper III, Paper V, and Paper VI, while in Paper IV only ROI analysis was conducted due to the low sample size. SPM was selected over FreeSurfer, another common neuroimaging software package. FreeSurfer estimation of hippocampal volume has been found to compare favorably with manual segmentation in young healthy populations, but has been found to overestimate hippocampal volume in older populations where hippocampal volume is reduced (Wenger et al., 2014). Given that hippocampal volume is also reduced in PTSD (Karl et al., 2006; Kitayama et al., 2005; Kühn & Gallinat, 2013), we did not conduct FreeSurfer analysis due to concerns that it may overestimate hippocampal volume in clinical populations. Although it was beyond the scope of the current dissertation, future work may seek to test this empirically and compare the reliability of FreeSurfer, SPM and manual segmentation estimates of hippocampal volume in PTSD.

In addition, MRI data acquisition may be subject to confounds and measurement error. For example, positioning of the participant within the head coil and scanner can influence

estimates of gray matter volume in the acquired image, although we attempted to control for this by ensuring that participants were positioned similarly in the head coil at the isocentre of the magnet and prior to image collection the slice angle was manually aligned to the genu-splenium of the corpus callosum along the sagittal axis. Variations in hormonal levels and caffeine intake may also influence estimates of gray matter volume, for example levels of female gonadal hormones are known to influence hippocampal volume. With the exception of *Paper II*, we did not include female participants. However, the role of gonadal hormones on brain structure in males has not been fully assessed and future work is needed. To control for the effects of caffeine, participants were asked to avoid caffeine on the day of scanning.

Symptom exaggeration

Analysis of symptom exaggeration or malingering, as presented in *Paper VI,* was not originally intended to form part of this dissertation. Rather, this arose out of discussions with the psychologists and psychiatrists I collaborated with at the German Federal Defense Force. As such, the data were not optimally designed to address such a question, resulting in the unequal number of credible patients and malingerers. In addition, as SVT data was not available for all patients, we did not exclude individuals with invalid or missing SVT test scores from the analyses of *Paper III, Paper IV* and *Paper V*, as this would have further reduced our sample sizes, which were, as previously discussed, already small. This is particularly relevant for *Paper IV* and *Paper V*, where aggravators may show less therapy-related improvements at both the neural and psychological level. Nevertheless, we did observe significant improvements in both hippocampal volume and reported symptomatology following therapy in both *Paper IV* and *Paper V*. This may be due to the fact that the number of aggravators was low in each study, and there were roughly equal numbers of identified malingerers in each group. Although this does not negate the problem, it may help to mitigate the effect of including some malingerers along with a majority of credible patients in our analyses. One should note that future studies seeking to replicate our findings in populations

of credible patients only could hope to observe stronger effects, similar to the ones we observed, given that these were in line with our hypotheses and fit well to the majority of existing literature.

Cross-sectional data

In *Paper I* and *Paper II* we correlated measures of stress exposure with gray matter volume and found that higher stress exposure correlates with smaller prefrontal gray matter volume. We hypothesized, based on previous animal work, that increases in stress exposure lead to decreases in gray matter volume, potentially via increases in stress-related hormones, reductions in neurogenesis, and increases in dendritic atrophy. In these analyses, we assumed that inter-individual differences may serve as a useful proxy for intra-individual change, although this cannot be directly assessed with the current data. In addition, due to the cross-sectional nature of the data, the directionality of these effects remains unspecified. Future studies should seek to employ a longitudinal design, to clarify whether increases in stress exposure do indeed lead to subsequent decreases in prefrontal gray matter.

Generalizability

Generalizability of the current findings may be limited by the specific nature of the population. With the exception of *Paper II*, all studies assessed Caucasian combat-exposed male soldiers in early- to mid-adulthood. Future studies may seek to explore how the current findings extend to female, non-military, pediatric and older-adult populations, and to other types of trauma. However, in *Paper II* we correlated stress exposure with gray matter volume in an adolescent civilian sample of males and females of Latino, East Asian or African American ethnicity, and found similar effects to those we observed in *Paper I*, in an early to mid-adulthood male-only Caucasian military sample. This initial replication in an unrelated sample gives a promising early indication that the results of this dissertation may generalize to other populations.

Sex and gender

Both biological sex and culturally defined gender may play a role in the effects of stress on the brain. At a biological level, sex differences are observed in neural responses to stress (McEwen & Morrison, 2013), while changes in the level of gonadal hormone during menstruation influence brain structure and function (Lisofsky, Mårtensson, et al., 2015; Lisofsky, Lindenberger, et al., 2015). In addition, an individual's gender can influence both the type of stress an individual will encounter and how that stress is socially and culturally defined. Specific types of trauma associated with higher rates of PTSD, such as domestic violence or sexual assault, are more likely to be experienced by women (Brewin et al., 2000; Kaminer et al., 2008; Kilpatrick et al., 2003), and the cultural meaning associated with being a victim of such an assault may also differ between genders (Sable, Danis, Mauzy, & Gallagher, 2006). Future work in mixed-gender and female-only samples is required to examine if and how the effects of stress on the brain, behavior, and cognition differ in men and women.

Motivation

In *Paper IV* and *Paper V* we measured the effects of therapeutic interventions on psychological symptoms and brain volume. Behavioral outcomes and neural changes are likely to be dependent on the individual participant's level of motivation, while therapeutic efficacy is known to be mediated by interpersonal factors between the therapist and patient (Lambert & Barley, 2001; Shedler, 2010). Future studies may seek to include measures of motivation and satisfaction with therapeutic interventions, to address how these may mediate effects on the brain.

Neural mechanisms

We observed increases in hippocampal volume following therapeutic interventions for PTSD, however the neural mechanisms underlying these increases remain unclear. MRI, although highly useful in assessing gross volumetric change, is not equipped to address questions regarding the underlying biological mechanisms that may drive it. For example, increases in hippocampal volume may be driven by angiogenesis, gliogenesis, synaptogenesis,

neurogenesis, or a complex combination of these processes (Zatorre, Fields, & Johansen-Berg, 2012). Future work may seek to assess hippocampal subfield volumes using high-resolution neuroimaging, which could indicate if these increases are driven more by dendritic arborization or neurogenesis. In addition, measures of diffusivity using diffusion weighted imaging could indicate if volumetric increases are associated with alterations in tissue density, indicating growth of cell tissue, or if tissue density remains stable, indicating dendritic growth (Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013).

Recent work with multiple neuroimaging assessments has demonstrated a period of expansion followed by renormalization during training interventions (Wenger et al., 2016). In *Paper IV* and *Paper V*, participants were assessed twice, prior to therapy and following therapy, with an interval of approximately six weeks between assessments. Previous work has demonstrated that after a period of six weeks, gray matter volume has already begun to renormalize following initial expansion (Wenger et al., 2016). Therefore, therapeutic interventions may have larger or wider effects on the brain at earlier stages in the intervention. Incorporating additional assessments during the therapy period would allow closer tracking of therapy-related gains and may reveal greater effects than those currently observed. Assessing the trajectory of change may also help illuminate the underlying mechanisms. If changes in hippocampal volume are driven by intervention-related gains, one may expect to see an inverted U-shape, representing a period of initial growth followed by renormalization. However, if changes in hippocampal volume are driven by recovery of lost volume following cessation of stress, one may expect to see a gradual increase in hippocampal growth throughout therapy, without a period of subsequent renormalization.

Therapeutic mechanisms

With regards to the Tetris intervention, the therapeutic mechanisms are unclear. One possibility is that video gaming leads to increases in hippocampal volume (Kühn et al., 2014) and that these increases lead to reductions in symptoms through general improvements in

memory and cognition (Vermetten et al., 2003). Alternatively, by playing Tetris directly following each therapy session, the reconsolidation of the traumatic memory may be interrupted via competition for cognitive resources (Holmes et al., 2009), leading to a weakened memory trace and fewer and less vivid subsequent intrusive memories. It may also be that a combined intervention, targeting both hippocampal volume and memory reconsolidation, is required to produce improvements in the persistent and debilitating symptoms that characterize PTSD. Future work may seek to distinguish these processes and assess each independently, for example by employing an intervention aimed at increasing hippocampal volume that does not also target reconsolidation, such as physical exercise.

In addition, playing Tetris may also serve a slightly more prosaic, but no less important function. During each psychotherapy session, the patient is asked to focus on the traumatic memory, along with all accompanying emotional sensations, and this imaginal exposure has been shown to exacerbate symptoms in some cases (Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002). A period at the end of each session is dedicated to closing the session, and reducing the emotional distress that has been elicited due to the reactivation of the traumatic memory. Anecdotal reports from both clinicians and patients suggest that this process is not always fully effective, and some residual emotional arousal is still present after the therapy session has ended. Playing Tetris may thus help to reduce the experience of distress following therapy by providing a distraction, although we did not test this empirically.

5.3. Conclusions and Outlook

This dissertation is presented with the aim of addressing several key questions in the field of stress and PTSD neuroimaging.

Paper I and *Paper II* both present clear evidence that smaller prefrontal gray matter volumes relate to stress exposure in subclinical populations. The implication of this finding is that the distinction between clinical and subclinical populations may not always be justified, and a more nuanced, continuous approach regarding stress exposure and stress-related symptomatology may yield useful insights. This approach has the dual benefits of increasing the population pool from which to recruit participants, as well as increasing real-world validity, as the majority of stress-exposed individuals will not go on to meet the criteria for a clinical diagnosis of PTSD, despite experiencing some level of psychological distress or cognitive impairment.

Results from *Paper III* detail functional and neural differences in emotion regulation between individuals with PTSD and trauma-exposed controls in emotion regulation. Emotion regulation is known to be impaired in PTSD, and the inability to effectively down-regulate negative emotion may play a role in the development and maintenance of symptoms and psychological distress following trauma exposure. Emotion regulation research distinguishes between adaptive, or effective strategies that target an emotional response before it occurs, such as cognitive reappraisal, and maladaptive, or ineffective strategies that target an emotional response once it has already begun, such as expressive suppression. Specifically, differences observed in the current work between PTSD patients and trauma-exposed controls relate to the timeline of neural activity during cognitive reappraisal, while no differences were observed during expressive suppression. These findings have implications for our understanding of the etiology and treatment of PTSD. In addition, by distinguishing between preparatory and active emotion regulation phases, and by distinguishing between different

regulation strategies, these findings provide greater granularity of detail regarding the neural dynamics of emotion regulation than previously described.

Paper IV and *Paper V* describe recovery-related gains in PTSD. Specifically, increases in hippocampal volume are observed following therapeutic interventions for PTSD. Results in *Paper IV* describe, for the first time, hippocampal volume increases following psychotherapy in medication-free individuals. Building upon the initial pilot study of *Paper IV*, *Paper V* then tests a novel therapeutic intervention, in the form of playing Tetris, as an adjunct to psychotherapy. Playing Tetris led to increases in hippocampal volume, and these increases correlated with reductions in PTSD, depression, and anxiety symptoms. This finding provides first evidence of the neural and behavioral benefits of a Tetris intervention for individuals with current PTSD. Given that PTSD is known to have a relatively poor long-term prognosis, demonstrating the utility of a cheap and practical adjunct to therapy that improves a wide range of long-term psychological outcomes has significant clinical implications.

Paper VI provides a note of caution for neuroimaging studies of PTSD, including our own. PTSD is vulnerable to the simulation or exaggeration of symptoms, as diagnosis is based on the individual's self-reported levels of symptoms and because individuals may be incentivized to seek a diagnosis, for example to receive financial compensation. The use of SVTs to assess the credibility of an individual's clinical presentation is recommended in PTSD, but in the majority of neuroimaging studies a diagnosis of PTSD is taken at face validity. In addition, no previous work has compared credible PTSD patients to malingerers at a neural level. *Paper VI* demonstrates that malingerers show larger gray matter volumes in regions implicated in PTSD, inhibition and deception. These results have implications for future work and for the interpretation of previous findings. Studies of PTSD that have failed to observe predicted effects, or have found results that conflict with the wider literature, may have been confounded by an unknown mix of credible patients and malingerers. In addition, the use of SVTs should be routinely incorporated into future studies of PTSD, as malingerers

differ from credible PTSD patients, both in regions similar to those in healthy controls, which will reduce the ability to detect differences between these groups, and in regions not traditionally associated with PTSD or stress, which may lead studies with a particularly high number of malingerers to report results that reflect the effects of symptom exaggeration rather than PTSD.

In summary, this dissertation contributes to the field of stress research in several distinct ways. It questions the current dichotomy between clinical and subclinical populations in neuroimaging research, and indicates instead that a more nuanced, continuous approach should be adopted. In addition, future work should more critically assess how results can distinguish the effects of stress in general from PTSD specifically. It adds new knowledge on the potential functional and neural factors that may underlie the development of PTSD, and provides greater granularity regarding the neural dynamics of emotion regulation in PTSD. It provides evidence of recovery of hippocampal volume in response to established and novel therapeutic interventions for PTSD, with implications for treatment of PTSD. Finally, it provides a word of caution to neuroimaging studies of PTSD, including our own, that a PTSD diagnosis should not be taken at face value, and tests to ensure the validity of symptoms be incorporated to ensure robustness and reliability of findings.

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7. Original Papers

Paper I

Butler, O., Adolf, J., Gleich, T., Willmund, G., Zimmermann, P., Lindenberger, U., Gallinat, J., Kühn, S. (2017). Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population. *Translational Psychiatry*, doi: 10.1038/tp.2016.288

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ORIGINAL ARTICLE

Military deployment correlates with smaller prefrontal gray matter volume and psychological symptoms in a subclinical population

O Butler[1], J Adolf[1], T Gleich[2], G Willmund[3], P Zimmermann[3], U Lindenberger[1,4,5], J Gallinat[6] and S Kühn[1,6]

Research investigating the effects of trauma exposure on brain structure and function in adults has mainly focused on post-traumatic stress disorder (PTSD), whereas trauma-exposed individuals without a clinical diagnoses often serve as controls. However, this assumes a dichotomy between clinical and subclinical populations that may not be supported at the neural level. In the current study we investigate whether the effects of repeated or long-term stress exposure on brain structure in a subclinical sample are similar to previous PTSD neuroimaging findings. We assessed 27 combat trauma-exposed individuals by means of whole-brain voxel-based morphometry on 3 T magnetic resonance imaging scans and identified a negative association between duration of military deployment and gray matter volumes in ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (ACC). We also found a negative relationship between deployment-related gray matter volumes and psychological symptoms, but not between military deployment and psychological symptoms. To our knowledge, this is the first whole-brain analysis showing that longer military deployment is associated with smaller regional brain volumes in combat-exposed individuals without PTSD. Notably, the observed gray matter associations resemble those previously identified in PTSD populations, and concern regions involved in emotional regulation and fear extinction. These findings question the current dichotomy between clinical and subclinical populations in PTSD neuroimaging research. Instead, neural correlates of both stress exposure and PTSD symptomatology may be more meaningfully investigated at a continuous level.

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INTRODUCTION

Stress is a pervasive element of modern life, and the detrimental effects of stress on physical and mental health[1–3] have long been recognized. On a neural level, the neurotoxic effects of stress are known to contribute to gray matter alterations in animals.[2,4] Chronic stress, or the administration of glucocorticoids, has been shown to result in volumetric reductions in hippocampal and prefrontal regions including the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC) through reductions in neurogenesis and dendritic atrophy.[5–7] More recently, neuroimaging methods have allowed *in vivo* investigation of the effects of stress on the structure and function of the brain in humans.

Neuroimaging research into the effects of stress in humans has focused mainly on post-traumatic stress disorder (PTSD). PTSD is a debilitating psychiatric disease characterized by intrusive memories, hyperarousal, emotional numbing and avoidance.[8] Research on PTSD has reported similar findings to those on stress in animal studies, including smaller gray matter volumes in hippocampal and prefrontal brain regions.[9–13] A key role for these regions in PTSD symptomatology is supported by their well-established role in memory function,[14] executive control processes,[15] emotion regulation and fear extinction.[16,17] However, it is an open question in the PTSD neuroimaging literature whether locally reduced gray matter volume represents a pre-existing risk factor, or is acquired, either following stress exposure or with the onset of symptomatology. First evidence from twin studies suggests that reduced hippocampal volumes represent a risk factor for PTSD,[18] whereas prefrontal reductions are acquired.[19]

Trauma exposure is a necessary condition for the development of PTSD.[20] However, the effects of trauma exposure on brain structure, in individuals who do not meet a clinical threshold, remain largely unexplored. Neuroimaging research on subclinical individuals is needed to clarify whether previously observed gray matter differences reflect a dichotomy between patient populations and trauma-exposed controls, or rather a spectrum of stress-related brain changes. The latter seems more likely, given evidence of a dose–response relationship between stress exposure and PTSD, with previous traumas, severity of trauma and additional life stress all posing significant risk factors for PTSD.[21] In functional neuroimaging research, results suggest that trauma exposure can have enduring effects on the brain, even in individuals without PTSD.[22]

Military deployment is one specific instantiation of exposure to repeated stress and trauma. In recent years, military and political conflict across the globe has increased, resulting in greater numbers of individuals experiencing combat and continuous exposure to extreme stress. In addition to acute stressors, there is

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growing recognition of non-specific deployment related 'wear and tear' as a source of stress injury.[23] Military deployment has many elements that may contribute to wear and tear, including separation from family and loved ones, disturbances to sleeping patterns, changes in diet, and limited opportunity for rest. In addition, deployed military personnel are also exposed to traumatic events, loss or grief, potential moral conflict between their ethical beliefs and the reality of their combat experiences, or a combination of these factors.

Neuroimaging research in this field has focused almost exclusively on clinical populations. However, only a fraction of individuals will actually develop PTSD during or after military deployment, with prevalence of post-deployment PTSD varying by severity of exposure and population characteristics.[24–27] In previous work assessing rates of PTSD in German soldiers, 85% of soldiers deployed overseas suffered at least one traumatic event. However, the incidence of first-time PTSD in the 12 months following return from deployment was only 0.9%,[27] whereas overall rates of PTSD in German troops range between 0.6 and 2.9%.[26,27] With rates of around 300 cases of PTSD for every 10 000 returning German soldiers,[27] the current sample of combat trauma-exposed individuals without psychopathology represent the majority of deployed individuals within the German Armed Forces. By focusing on a non-clinical population that has been exposed to trauma, the current study addresses an important gap in neuroimaging research into stress and PTSD.

In this study, we thus examined brain-structural correlates of military deployment in a non-clinical population using magnetic resonance imaging (MRI). We chose duration of military deployment in days as an objective and verifiable measure of stress exposure that is directly comparable across individuals. We consider this to be more robust than a measure such as combat experiences, which relies on recollection months or years after an event has occurred, and which fails to capture the non-specific effects of deployment related 'wear and tear'. We also consider military deployment in days to be a more stable measure of stress exposure than PTSD questionnaire scores, which assess symptoms experienced over the last week or month. Trauma is known to produce lasting effects on the brain.[28] Therefore, the more stable the measure of stress exposure, the more likely it will capture the long lasting effects of stress on brain. We examined whether smaller gray matter volumes previously observed in PTSD populations are also present in individuals exposed to combat trauma who did not receive a psychiatric diagnosis. We also explored associations between military deployment, gray matter volume and PTSD symptoms. We hypothesize that as stress exposure—as indexed by duration of military deployment—increases, gray matter volume in regions previously implicated in PTSD—namely the vmPFC, ACC and hippocampus—decreases. In addition, based on previous research demonstrating a mediating role of gray matter between stress exposure and psychological distress,[3,18,29–31] we hypothesize that alterations in gray matter will correlate more strongly than military deployment with PTSD symptoms.

MATERIALS AND METHODS

Participants

Twenty-eight male soldiers with mission-related trauma but without mental illness were recruited from the German Federal Armed Forces. All participants had been deployed overseas to areas of conflict and were screened by clinical psychologists for the presence of mission-related trauma within the last 2 years (inclusion criteria) and for current or previous Axis I psychiatric disorders (exclusion criteria) according to ICD-10 criteria[20] using the Mini-DIPS.[32] The Mini-DIPS is a well-established structured interview for point and lifetime prevalence of AXIS I disorders and has been shown to be valid and reliable for the diagnosis of mental disorders.[32] The local Ethics Committee of Charité University Clinic, Berlin, Germany, approved of the study, and written informed consent was obtained from each participant prior to participation. One participant was identified as an age outlier (Z-score $> \pm 2.5$) and excluded from subsequent analysis. The mean age of the remaining 27 participants was 32.33 years (s.d. 5.3, ranging between 23 and 42). Participants had completed on average 3.4 military deployments (s.d. = 2.6, ranging between 1 and 11), with an average total of 363 days of military deployment (s.d. = 246, ranging between 22 and 900) in their military career. This sample size allowed us to detect large effects ($r \geqslant 0.5$), at $\alpha = 0.05$ and 80% power[33] as can be expected based on a previous meta-analysis of PTSD neuroimaging studies.[12]

Scanning procedure

Structural images were collected on a Siemens Tim Trio 3T scanner (Erlangen, Germany) using a standard 12-channel head coil. The structural images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI protocol (www.adni-info.org; repetition time = 2500 ms; echo time = 4.77 ms; TI = 1100 ms, acquisition matrix = 256 × 256 × 176, flip angle = 7; 1 × 1 × 1 mm^3 voxel size).

Questionnaires

Prior to neuroimaging all participants completed a number of questionnaires assessing psychological symptoms and experiences during deployment. Participants completed German versions of the following self-report questionnaires (see below for details); the Post-traumatic Diagnostic Scale (PDS), the Brief Symptom Inventory (BSI), the Interpretation of PTSD Symptoms Inventory (IPSI) and the Posttraumatic Cognitions Inventory (PTCI), as well as a study-specific questionnaire that included items on the number and duration of military deployments.

The PDS[34] is designed to aid in the diagnosis of PTSD according to the DSM IV criteria and assess symptom severity. As part of the PDS respondents rated 17 items representing the main symptoms of PTSD experienced in the past 30 days, on a four-point scale.

The BSI[35] is a 53-item self-report questionnaire measuring nine symptom dimensions of psychological distress (for example, somatization, depression, anxiety and hostility). Each item was rated on a five-point scale ranging from 0 (not at all) to 4 (extremely), based on the intensity of distress over the past week. For the BSI, we utilize the Global Severity Index (GSI) score, as this is recommended as the single best indicator of current psychological distress levels.[35] The GSI is calculated by taking the mean of the nine subscales.

The IPSI[36] assesses appraisal of PTSD symptomatology over the past month, rated from 1 (totally disagree) to 7 (totally agree).

The PTCI[37] is a 33-item questionnaire on negative post-trauma appraisals over the past month, relating to the self, the world, and self-blame, rated from 1 (totally disagree) to 7 (totally agree).

A summary score across all four symptom-oriented questionnaires was also calculated. This is appropriate from a theoretical perspective because all four questionnaires are designed to assess trauma-related symptoms and psychological distress, and also justified empirically, given that the four questionnaire scores correlated positively among each other.

Data analysis

Structural data were processed with voxel-based morphometry (VBM8, http://dbm.neuro.uni-jena.de/vbm.html) and statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) using default parameters running on MATLAB 8.1 (Mathworks, Sherborn, MA, USA). VBM is a neuroimaging analytic technique that allows whole-brain investigation of focal differences in brain anatomy based on statistical parameter mapping of structural images. It involves bias correction, tissue classification, and affine registration. Images were normalized to Montreal Neurological Institute (MNI) space and segmented into gray matter, white matter and cerebrospinal fluid based on voxel signal intensity and *a priori* expectation of tissue type based on anatomical location, using default parameters. Modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, the analysis of modulated data tests for regional differences in the absolute amount (volume) of gray matter. Images were smoothed with a full width at half maximum (FWHM) kernel of 8 mm.

A whole-brain voxel-wise multiple regression with days of deployment was computed. Age and total gray matter volume were entered as

covariates of no interest. Total gray matter volume was used as a covariate of no interest to control for global differences in gray matter and to increase the specificity of regional effects.[38] The resulting maps were thresholded at $P < 0.001$ and cluster-extent thresholded with family-wise error (FWE) correction at $P < 0.05$ in combination with correction for non-isotropic smoothness[39] to control for type-I error.

The Region-of-Interest Extraction (REX) Toolbox[40] was used to extract gray matter volumes from the resultant clusters, creating one value per participant per cluster.

To explore the relationship between military deployment and related gray matter volumes to psychological symptoms, zero-order bivariate correlations between deployment-related gray matter volume, days of deployment, age and the mean score of the four symptom-oriented questionnaires were estimated. OpenMx 2.2.4 [ref. 41] under R 3.2.1 [ref. 42] was used to obtain maximum likelihood point estimates of the correlations and, importantly, 95% likelihood-based confidence interval estimates. Likelihood-based intervals perform relatively well in samples of small size and are sensible given bounded parameter spaces as is the case with correlations.[43] Indeed, a quick simulation with 10 000 replications for a sample size of 27 cases and a correlation matrix similar to the one estimated here, reveals very good coverage rates of above 94% per parameter. To ease optimization, the data were *z*-standardized prior to analysis, correcting for the extreme intervariable differences in scale and location.

RESULTS

Participants reported an average symptom severity score on the PDS of 4.26 (s.d. = 3.99, ranging between 0 and 16). A symptom intensity score between 1 and 10 is considered mild, whereas a score of between 11 and 20 is considered moderate. None of the participants met all the criteria for PTSD according to the PDS, further supporting the clinical assessment of these individuals as without psychopathology. For the BSI, we utilize the GSI score.[35] A T score of 63 or above on the GSI is considered clinically significant, whereas the mean for our current population was 38.15 (s.d. = 10.95, ranging between 24 and 70). For the IPSI a clinically significant score for individuals with PTSD is 3.4 (±1), whereas the mean score among the participants was 1.9 (*s.d.* = 0.55, ranging between 1.36 and 3.54). For the PTCI we used the total score, which is the sum of the individual scores for the 33 statements. In the original paper by Foa *et al*., the score for individuals with PTSD was 133 (±44), while the score for traumatized individuals without PTSD was 49.[37] The mean of our current sample, 48.07 (s.d. = 15.07, ranging between 33 and 90), reflects our recruitment criteria.

Whole-brain regression analysis yielded a significant negative association between days of deployment and gray matter volume in left vmPFC (MNI coordinate peak voxel $x = -9$, $y = 63$, $z = 22.5$; $P < 0.05$, $k = 405$, FWE cluster-extent threshold corrected) and in bilateral dorsal ACC ($x = 3$, $y = 7.5$, $z = 43.5$; $P < 0.05$, $k = 290$; Figure 1a). No region showed a significant positive association between gray matter and days of deployment. For visualization purposes, a scatterplot shows the combined gray matter volume for both regions plotted against days of deployment (Figure 1b).

In order to test the robustness of the result, leave-one-out cross validation analysis was conducted. The analysis was re-run 27 times with 26 participants, excluding a different participant each time. The resulting maps were thresholded at $P < 0.001$ and cluster-extent thresholded with FWE correction at $P < 0.05$ in combination with correction for non-isotropic smoothness. A one-sample *t*-test was conducted on the corrected maps from the negative correlation between days of deployment and gray matter volume. The resulting clusters were also located in the left vmPFC (MNI coordinate peak voxel $x = -1.5$, $y = 48$, $z = 7.5$, $P < 0.05$, $k = 361$, FWE cluster-extent threshold corrected) and bilateral dorsal ACC ($x = -1.5$, $y = 6$, $z = 43.5$, $P < 0.05$, $k = 175$, FWE cluster-extent threshold corrected). No positive correlation between days of deployment and gray matter volume survived in any of the analyses.

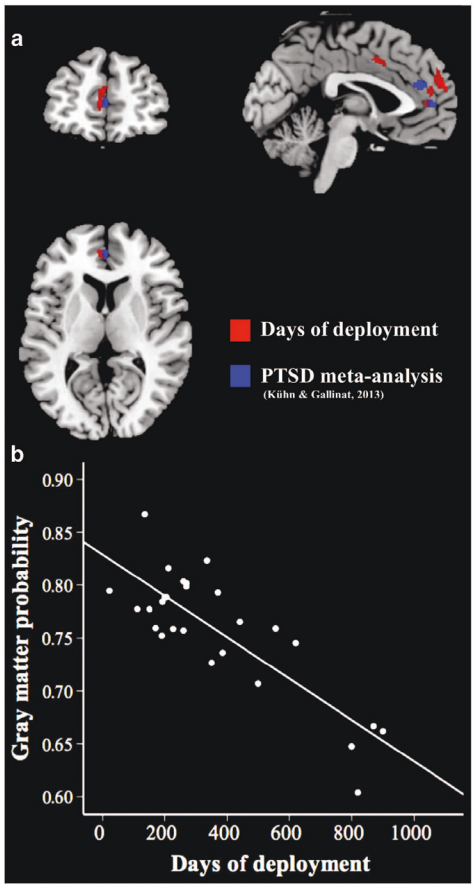

Figure 1. (**a**) Brain regions showing a significant negative correlation between military deployment and gray matter volume in left ventromedial prefrontal cortex (vmPFC; MNI coordinates: $x = -9$, $y = 63$, $z = 23$; $P < 0.05$, $k = 405$, family-wise error and non-stationary smoothness corrected) and in bilateral dorsal anterior cingulate cortex (ACC; MNI coordinates: $x = 3$, $y = 8$, $z = 44$; $P < 0.05$, $k = 290$) are shown in red. Structural reductions from a meta-analysis comparing patients with post-traumatic stress disorder (PTSD)[13] with controls are shown in blue. (**b**) The scatterplot depicts the correlation between the combined gray matter probability values of the two regions per individual and days of deployment. MNI, Montreal Neurological Institute.

We failed to observe a predicted correlation between hippocampal volume and days deployment, even at a more lenient significance threshold of $P_{(\text{uncorrected})} < 0.001$.

The correlations between the psychological symptom score (that is, the summary score on the four symptom-oriented questionnaires), deployment-related gray matter volume from the clusters identified in the vmPFC and ACC, days of deployment, and age are shown in Figure 2.

The psychological symptoms score was significantly negatively associated with gray matter volume (that is, the corresponding confidence interval excludes zero) but did not show a reliable association with days of deployment. Although in the latter case one might speak of a trend towards a positive effect, as the lower interval boundary was close to zero. The correlation between deployment-related gray matter volume and days of deployment

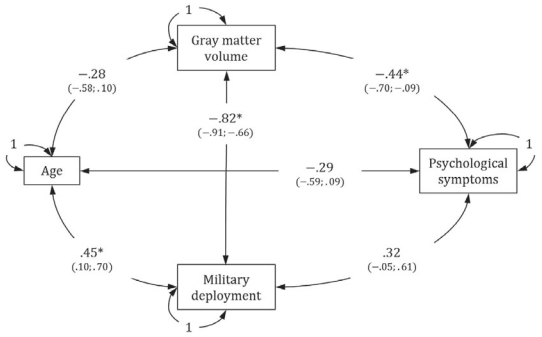

Figure 2. Correlations between psychological symptoms, deployment-related gray matter volume from clusters identified in the ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC), days of deployment, and age. Maximum likelihood point estimates are reported along with 95 percent likelihood-based confidence interval estimates in brackets. *$P < 0.05$; note that a 95% confidence interval estimate excluding zero implies that the corresponding effect is significantly different from zero at a significance level of 0.05.

reflects the results also described in the whole brain regression analysis. Note that the confidence intervals were generally wide (that is, the correlation point estimates are relatively imprecise), reflecting the small size of the sample. No effect was found for age.

DISCUSSION

In the present study, we investigated the neural and behavioral correlates of repeated stress exposure in trauma-exposed soldiers. Individuals with longer histories of military deployment showed smaller volumes in the left vmPFC and bilateral dorsal ACC. The regions observed in the current study overlap directly with those previously observed to be smaller in a PTSD meta-analysis, where trauma-exposed healthy controls were compared with PTSD patients.[13] The current findings provide support for the detrimental effects of stress exposure on gray matter volume, also in subclinical populations and have two main implications. First, they point towards a reduction of prefrontal gray matter in response to environmental stressors. This may indicate that at least some of the smaller gray matter volumes observed in PTSD represent a consequence of, rather than a risk factor for, stress exposure and stress related psychopathology. However, longitudinal research is required to establish the directionality and nature of these effects. Secondly, as stress exposure in subclinical individuals increases, a pattern of smaller prefrontal gray matter emerges, similar that observed in PTSD patients. This has important implications for future neuroimaging studies of stress exposure and PTSD. The current dichotomy between individuals with and without a clinical diagnosis may not be supported at the neural level, and instead neural correlates of both stress exposure and symptomatology may be more meaningfully investigated at a continuous level.

In functional MRI studies the vmPFC and dorsal ACC have been implicated in affective and cognitive processing, respectively, including the regulation of fear expression, memory and emotional processing.[44] Structural reductions in these two related but functionally distinct regions could explain the dual psychopathologies observed in PTSD: affective symptoms such as hyperarousal and numbing[8] as well as cognitive symptoms including memory deficits[45,46] and failure to learn fear extinction.[14,17]

Specifically, the vmPFC is known to have a key role in self-referential processing and the extinction of conditioned fear. A neurocircuitry model of PTSD[47] proposes that there is a failure to inhibit a fear reaction in response to threat, through reduced top–down control by the vmPFC and reduced bottom–up control by the hippocampus on the amygdala.[48] In an earlier study by this group,[49] fMRI was used to assess blood flow while participants were shown images of happy and fearful faces. Patients with PTSD showed increased amygdala and reduced medial PFC responsivity to fearful versus happy facial expressions, compared with controls. In addition, PTSD symptom severity was negatively correlated to activity in the medial PFC during this task.[49]

On the other hand, the ACC is involved in multiple processes, including modulation of affect, memory, response to pain, autonomic and endocrine functions and visceral responses.[50,51] The dorsal ACC is a proposed cognitive subdivision of the ACC, forming part of the attention network and involved in the modulation of attention, motivation, error detection and working memory,[52] as well as modulating fear expression.[53] Gray matter reductions in the dorsal ACC have previously been observed in PTSD populations exposed to both single-event trauma (due to a terrorist attack)[54] and chronic (abuse-related) trauma.[55]

We did not observe a correlation between hippocampal volume and days of deployment. Some evidence suggests that smaller hippocampal volumes may only be present in individuals with severe or chronic PTSD. In some studies smaller hippocampal volumes in PTSD patients versus controls were only observed when individuals with less severe PTSD were excluded from the analysis,[18] while other studies including patients with less severe PTSD failed to find smaller hippocampal volumes.[56,57] Another possible explanation for the divergence of findings may be that a smaller hippocampal volume may constitute a risk factor for PTSD. In a study of monozygotic twins discordant for combat exposure, Vietnam veterans with PTSD and their non-combat exposed co-twins had smaller hippocampal volumes than those of combat exposed non-PTSD veterans and their co-twins.[18] This finding suggests that smaller hippocampi are not the result of traumatization but rather constitute a risk factor for PTSD. PTSD symptom severity of the exposed twin was also negatively correlated with hippocampal volumes of the non-exposed twin. This was taken as evidence that smaller hippocampal volumes may precede stress exposure and increase risk for psychopathology. In contrast, a later study on the same data suggested that reduced gray matter in regions including the ACC represent stress-induced loss, with veterans with PTSD showing smaller volumes than their non-combat exposed co-twins or combat veterans without PTSD.[19]

In the current study, we observed correlates of military deployment in a subclinical population that mirror previous findings in populations with diagnosed PTSD, including research that compared individuals with PTSD to combat trauma-exposed controls (that is, participants similar to those examined here). In contrast to our study, most combat PTSD neuroimaging research examines data from participants with a long interval between combat exposure and assessment. In a meta-analysis of PTSD studies reporting smaller gray matter volume in PTSD, five of the six combat-related studies included reported an interval of over ten years between trauma and assessment.[11] The remaining study, which did not report the duration of the interval, failed to show evidence of hippocampal atrophy.[58] In the current study there was a relatively short period between combat-related stress exposure and assessment (less than two years). It may be that over longer periods, healthy individuals recover gray matter, while individuals with psychopathology do not.

On the basis of prior knowledge about detrimental effects of stress on brain structure[7] and predictive links of smaller gray matter volumes to PTSD,[18] symptom severity,[29] and response to therapy,[30] we hypothesized that combat exposure would lead to increased activation of the stress response, both during traumatic events, and through anticipation and expectation of such events. This increased stress activation would be expected to result in

altered brain chemistry and structure, leading to greater susceptibility to the psychological impact of events and subsequent psychological distress. In line with this assumption, we found that smaller deployment-related gray matter volumes in the vmPFC and ACC correlated with higher scores on the psychological symptom-oriented questionnaires. In addition, military deployment itself did not significantly correlate with psychological symptoms, emphasizing the utility of neuroimaging data over and above questionnaire data.

It needs to be kept in mind, however, that the reported associations between brain structure, military deployment, and psychological symptoms are cross-sectional in nature and represent between-person differences whose etiology has not been observed. Longitudinal data are needed to learn more about the temporal dynamics and possibly reciprocal causal effects among these variables. This would also help in studying potential links between pre-existing between-person differences and between-person differences in stress events, physiological reactivity, and distress. Of particular interest would be the question whether the effect of stress exposure per se on stress symptomatology is mediated by stress-related brain changes, and whether this mediation is modulated by pre-existing individual differences.

The potential mediating role of brain structure in the development of psychological symptoms also has implications for intervention. It has previously been shown that stress-related brain changes are reversible and can be altered by both pharmacological and psychological therapeutic interventions, as well as lifestyle interventions such as diet changes, exercise, rest, and stress avoidance.[31] Interventions aimed at recovering lost gray matter may protect against subsequent development of psychopathology. In addition, increases in gray matter may also correlate with increased response to therapy. Studies of PTSD patients scanned prior to therapy showed that larger gray matter volumes predicted better response to therapy and increased symptom reduction.[29,30] In addition, alterations in gene expression and increases in hippocampal volume have been observed in patients with PTSD following therapy, with increases in hippocampal volume predicting reductions in PTSD symptomatology.[59]

We recognize that the duration of military deployment is a broad index of stress exposure. However, we propose that it is nevertheless a conceptually useful variable that ties into current theories of stress injury, including wear and tear,[23] and allostatic load.[60,61] Duration of military deployment is also an objective and verifiable measure that does not rely on subjective interpretation months or years after an event has occurred, and is directly comparable across individuals.

CONCLUSION

To summarize, the present findings reveal associations between military deployment and gray matter volume among personnel without a clinical diagnosis of PTSD that are similar to those also observed in PTSD populations. To our knowledge, this is the first structural MRI study using VBM to provide evidence for an association between military deployment and gray matter in individuals with no current or previous psychopathology. The present findings, in the context of previous findings in patients diagnosed with PTSD, question the current dichotomy in the neuroimaging literature between clinical and subclinical populations. Indeed, trauma-exposed subclinical individuals may provide a useful and hitherto overlooked population when exploring the effects of stress on the brain, made all the more relevant by the fact that these individuals represent the majority of trauma exposed individuals. These results also underscore the need for future work to include objective and continuous measures of trauma exposure.

One potential limitation is the specific nature of the participant group and the generalizability of the current findings. Other adult populations with chronic stress exposure and high rates of PTSD, such as first responders, may also show similar changes in prefrontal gray matter, even in subclinical populations. Indeed, these results may also extend to single traumas, such as motor vehicle accidents or personal assault, and to individuals with high levels of perceived stress in their daily life. However, neural effects may be more pronounced in military populations as trauma sequelae are likely to be exacerbated during deployment by multiple exposures within a short period of time, and limited opportunity for rest. Future work is needed to explore how the current results extend to non-military and female samples.

In addition, the data point to a relationship between psychological symptoms, gray matter volumes in ACC and vmPFC, and military deployment. Further longitudinal research is necessary to disentangle the causal chain of effects, that is, whether increased stress exposure leads to altered brain structure, greater susceptibility to the psychological impact of events, and subsequent psychological distress.

CONFLICT OF INTEREST

JG has received research funding from the German Federal Ministry of Education and Research (BMBF), German Science Foundation (DFG), AstraZeneca, and speaker fees from Lundbeck, Janssen-Cilag, Lilly, and Otsuka. GW and PZ are employed by the German Armed Forces. Their employment had no influence on the study design. The remaining authors declare no conflict of interest.

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Paper II

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RESEARCH ARTICLE

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Community violence exposure correlates with smaller gray matter volume and lower IQ in urban adolescents

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Abstract

Adolescents' exposure to community violence is a significant public health issue in urban settings and has been associated with poorer cognitive performance and increased risk for psychiatric illnesses, including PTSD. However, no study to date has investigated the neural correlates of community violence exposure in adolescents. Sixty-five healthy adolescents (age = 14–18 years; 36 females, 29 males) from moderate- to high-crime neighborhoods in Los Angeles reported their violence exposure, parents' education level, and free/reduced school lunch status (socio-economic status, SES), and underwent structural neuroimaging and intelligence testing. Violence exposure negatively correlated with measures of SES, IQ, and gray matter volume. Above and beyond the effect of SES, violence exposure negatively correlated with IQ and with gray matter volume in the left inferior frontal gyrus and anterior cingulate cortex, regions involved in high-level cognitive functions and autonomic modulation, and previously shown to be reduced in PTSD and combat-exposed military populations. The current results provide first evidence that frontal brain regions involved in cognition and affect appear to be selectively affected by exposure to community violence, even in healthy nondelinquent adolescents who are not the direct victims or perpetrators of violence.

KEYWORDS
adolescent development, brain, post-traumatic stress disorder, stress, voxel-based morphometry

1 | INTRODUCTION

Community violence exposure is a significant public health issue for urban adolescent populations (Stein, Jaycox, Kataoka, Rhodes, & Vestal, 2003) and is linked to poorer cognitive (Delaney-Black et al., 2002; Sharkey, 2010) and psychological outcomes (Fowler, Tompsett, Braciszewski, Jacques-Tiura, & Baltes, 2009). Such criminal activity is vastly disproportionate across communities. In certain urban communities, such as those in South Los Angeles, children and adolescents are exposed to the highest rates of violent crimes per capita, with rates of up to 188 violent crimes per 10,000 people per year, compared with the citywide average of 29, and some areas that experience almost none (Los Angeles Times, 2017).

The detrimental effects of stress on physical and mental health have long been recognized (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2000; Selye, 1936). It has been shown that chronic stress leads to a continuous release of glucocorticoids, which is associated with reduced neurogenesis and increased dendritic atrophy (Lupien

et al., 2009). Volumetric reductions in regions particularly sensitive to the effects of glucocorticoids, such as the hippocampus (Sapolsky, Krey, & McEwen, 1985) and prefrontal cortex (Arnsten, 2009), have been related to chronic stress exposure (McEwen & Morrison, 2013; Sapolsky, Uno, Rebert, & Finch, 1990). This study focuses on community violence exposure as a form of chronic stress (for a review, see Tolan, 2016). This is supported by a wide body of literature demonstrating the negative effects of community violence at the cognitive (Delaney-Black et al., 2002; Sharkey, 2010), psychological (Fowler et al., 2009; Margolin & Gordis, 2000), and endocrinological levels (Aiyer, Heinze, Miller, Stoddard, & Zimmerman, 2014; Kliewer, 2006; Wilson, Kliewer, Teasley, Plybon, & Sica, 2002). Importantly, the strength of an individual's stress response is determined in part by the ability to predict upcoming events and to exert control over the situation (de Kloet, Joëls, & Holsboer, 2005). As such, community violence exposure is likely to elicit a strong stress response due to its unpredictability and the low level of control an individual can exert over the situation.

Community violence exposure is likely higher in youths from low socioeconomic status (SES) backgrounds due to criminal and gang activity in the neighborhoods in which these youths live, though some youths will have witnessed more than others. Adolescents spend more time outside of their homes and away from their parents/caregivers than do children, making it likely that the community social environment may especially impact them. Adolescence is also a critical period in development, during which time individuals are particularly sensitive to social stimuli (Albert, Chein, & Steinberg, 2013) and may be particularly susceptible to the effects of social-relational stress (Lupien et al., 2009). Adolescents, when compared with children or adults, show increased autonomic responses to social stress (Hollenstein, McNeely, Eastabrook, Mackey, & Flynn, 2012) and demonstrate increased and protracted release of stress-related hormones (Romeo et al., 2014; Stroud et al., 2009). In addition, brain regions known to be the most sensitive to stress in adulthood, including the hippocampus, prefrontal cortex, and amygdala, all continue to mature during adolescence (Giedd & Rapoport, 2010; Gogtay et al., 2004). Given this constellation of factors, it is very possible that violence exposure presents an additional liability for brain development in adolescence, beyond that known to be associated with SES (Noble et al., 2015).

Previous neuroimaging studies of pediatric stress exposure have demonstrated that adverse experiences during childhood and adolescence correlate with smaller hippocampal and medial prefrontal gray matter volumes (Andersen et al., 2008; Dannlowski et al., 2012; Van Harmelen et al., 2010), and may increase the risk for psychiatric illnesses in adulthood (Kaufman, Plotsky, Nemeroff, & Charney, 2000). The majority of neuroimaging studies on the effects of stress in pediatric and adult populations have used clinical samples, specifically posttraumatic stress disorder (PTSD). In a recent review of neuroimaging studies of child abuse (Hart & Rubia, 2012), 27 of the 29 structural magnetic resonance imaging (MRI) studies reviewed included participants with psychopathology, while the remaining two did not report psychiatric diagnoses. As these studies mainly used clinical samples, the results may be due to stress, the psychiatric condition, or an interplay between the two. In addition, the majority of pediatric stress exposure studies have investigated the effects of abuse and neglect experienced within the home during childhood and adolescence. In this study, we assessed healthy adolescents only, without any current or previous psychiatric diagnosis and without a history of abuse or neglect. We consider the current sample to represent an important extension of previous studies of stress exposure in human adolescents, as the effects observed should not be confounded by interactions with psychiatric disorders or factors related to abuse experienced within the home.

In this research, we tested whether community violence exposure correlates with cognitive ability and gray matter volume in a healthy nondelinquent adolescent population (participants recruited were in full-time education, passing all courses, and not the subject of disciplinary action; they reported no use of drugs or alcohol). We hypothesized that community violence exposure would correlate with lower IQ and reduced prefrontal and hippocampal gray matter in regions similar to those observed in childhood maltreatment and PTSD, even after controlling for SES (parental education levels and eligibility for free or reduced-price school lunch). Structural MRI, demographic, and cognitive ability data were collected. Whole-brain analysis and a region of interest approach were used to investigate the neural hypothesis.

2 | METHODS AND MATERIALS

2.1 | Participants

Sixty-five right-handed adolescents (55% female, 45% male; 45% Latino, 52% Asian American, 3% African American) were recruited from public high schools in low-SES Los Angeles neighborhoods (mean age = 15.8 years, $SD = 1.1$, ranging between 14 and 18). These neighborhoods have high levels of immigrants and all participants had at least one immigrant parent. Enrollment criteria included no history of neurological or psychiatric disorders, physical or emotional abuse or neglect, use of psychotropic medication, drugs or alcohol, or presence of a medical condition that would preclude scanning. Criteria also included full-time enrollment in school, passing all classes, and not under any disciplinary action. All participants and their parents gave written informed consent in accordance with the requirements of the Institutional Review Board of the University of Southern California (USC).

Prior to the study, adolescent participants filled eligibility questionnaires, and then they and their parents separately underwent structured private interviews to determine in more detail the status of the participant's home situation, emotional wellbeing, social relations at home and at school, drug and alcohol use, and future life plans. By their own confidential report, all reported stable, safe homes and relationships, and positive plans for the future. None of the participants reported any history of drug or alcohol use, none had perpetrated violence or other criminal acts, and none had been physically assaulted. All participants were therefore included in the analysis.

The neural and violence exposure data for the current study were collected as the first wave of a longitudinal project investigating

psychosocial and neurobiological aspects of social emotional development in adolescence. Sample size was determined to allow sufficient power to detect neurobiological effects. A sample size of 62 or higher would allow us to detect medium to large effect sizes ($r \geq .3$), with a voxel-wise threshold of $p < .005$, as can be expected based on a comparison of non-PTSD trauma-exposed individuals and healthy controls from a meta-analysis of PTSD neuroimaging studies (Karl et al., 2006).

2.2 | Community violence exposure

Cumulative lifetime community violence exposure was assessed via a 13-item modified version of the Survey of Children's Exposure to Community Violence – self-report version (Margolin et al., 2009). Given that no externally verifiable measure for individual community violence exposure exists, self-report arguably provides the best practical index, and is commonly used in studies of community violence exposure (McDonald & Richmond, 2008). Exposure to violence was measured by providing participants with a list of 13 events that involved either victimization (e.g., Item 9. Has anyone ever threatened to beat you up?) or witnessing and/or hearing about violence (e.g., Item 13. Have you ever witnessed or heard about someone being shot?), as previous work has demonstrated that both being a victim and being a witness must be considered to capture the full impact of violence exposure (Rosenthal, 2000). For each item, participants received a score from 1 ("Never") to 4 ("More than twice"), giving a potential final score of between 13 and 52. Participants scored an average 24.8 ($SD = 8.9$, ranging between 13 and 47) on the violence exposure questionnaire. After completing the questionnaire, each participant then underwent a private interview to confirm their answers and to determine whether the reported violence exposure occurred in the community (neighborhood or school), in the home, or in the media (e.g. on television). Incidents that happened in the home and involved family members would disqualify the participant (no incidents in the home were reported). Incidents witnessed in the media were not counted toward the violence exposure score.

2.3 | Socioeconomic status (SES)

All subjects were recruited from public schools in low-SES neighborhoods; however, to get insight into further variation within this sample, we also collected information on (1) whether participants received free or reduced-price school meals and (2) highest parental education level. The school meals program provides government-subsidized meals for students from financially low-resourced families (annual family income $\leq$130% of federal poverty line for free meals, $\leq$185% of federal poverty line for reduced-price meals; https://www.fns.usda.gov/school-meals/applying-free-and-reduced-price-school-meals). Forty-six participants reported receiving free meals, 5 reported receiving reduced-price meals, and 14 reported paying full price for meals. (As only 5 participants received reduced-price lunch, free and reduced-price categories were collapsed.) Following work by Noble et al. (2015), parental education level was recoded as years of formal education (Supporting Information, Table S1). Average reported parental education was 12.3 years, $SD = 3.9$, ranging between 8 and 18 years. Parental education data were missing from four Latino participants. Their parental years of education were imputed as the mean of Latino participants in their neighborhood (10 years of schooling).

2.4 | Cognitive ability

Participants completed the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II; Wechsler, 2013). Owing to funding and design considerations for the bigger longitudinal project, this was collected at a follow-up measurement, ~2 years following collection of the neural and violence exposure data. Participants had an average Full Scale IQ (FSIQ) score of 105.3 ($SD = 11.3$, ranging between 79 and 131). WASI data for 5 participants were not available, giving a final sample size of 60.

2.5 | MRI data acquisition

Structural images were collected on a Siemens 3 T MAGNETON TIM Trio scanner (Erlangen, Germany) with a 12-channel matrix coil at the Dana and David Dornsife Neuroimaging Center, University of Southern California. The images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) (repetition time = 2,530 ms, echo time = 3.09 ms, TI = 800 ms, acquisition matrix = 256 × 256 × 176, flip angle = 10°; 1 × 1 × 1 mm^3 voxel size).

2.6 | MRI data preprocessing

Prior to processing, raw images were visually inspected for motion artifacts, quality and gross anatomical abnormalities. In addition, following processing, segmented and normalized data were visually inspected. No issues with artifacts, data quality, anatomical abnormalities, or segmentation and normalization were identified. Structural data were processed with voxel-based morphometry (VBM8; http://dbm.neuro.uni-jena.de/vbm.html) and statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) using default parameters running on MATLAB 9.1 (Mathworks, Sherborn, MA). VBM is a neuroimaging analytic technique that allows whole-brain investigation of focal differences in brain anatomy based on statistical parameter mapping of structural images (Ashburner & Friston, 2000; Mechelli, Price, Friston, & Ashburner, 2005). Images were normalized to Montreal Neurological Institute (MNI) space and segmented into gray matter, white matter, and cerebrospinal fluid based on voxel signal intensity and a priori expectation of tissue type based on anatomical location, using default parameters. Modulation was applied to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. Images were smoothed with a full-width at half-maximum kernel of 8 mm.

2.7 | MRI data analysis

Statistical analysis was conducted on preprocessed gray matter images using SPM8.

2.8 | Whole-brain analysis

A whole-brain voxel-wise multiple regression with community violence exposure was computed. Whole-brain analysis allows for unbiased and unconstrained characterization of anatomy, rather than restricting analysis to a priori hypothesized regions of interest (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). Parental education level, eligibility for free/reduced price lunch, gender, ethnicity, age (in days), and total gray matter volume were included as covariates of no interest. Parental education level and eligibility for free/reduced price lunch were included to control for known effects of SES on brain development (Noble et al., 2015). Total gray matter volume was used as a covariate of no interest to allow detection of regional specific effects that are independent from global differences in gray matter volume (Mechelli et al., 2005; Peelle, Cusack, & Henson, 2012). Ethnicity was included to control for potential morphological differences between the ethnic groups (Bai et al., 2012; Chee, Zheng, Goh, Park, & Sutton, 2011; Isamah et al., 2010). Gender was included to control for differences in mean gray matter volume and developmental trajectories between males and females (Lenroot et al., 2007). An absolute gray matter probability threshold of 0.4 was applied. The resulting maps were thresholded at $p < .005$ at the voxel level and cluster-extent thresholded at expected voxels per cluster according to random field theory ($k = 205$) in combination with correction for nonisotropic smoothness (implemented in VBM 8; Hayasaka & Nichols, 2004) to control for type-I error at $\alpha = .05$.

2.9 | Region of interest (ROI) analysis

Separate anatomical masks for the bilateral hippocampus and amygdala were anatomically defined using the anatomical automatic labeling (AAL; Tzourio-Mazoyer et al., 2002) template. The Region-of-Interest Extraction Toolbox (REX; Whitfield-Gabrieli, 2009) was used to extract gray matter volumes from the identified clusters.

3 | RESULTS

3.1 | Socioeconomic status (SES)

Parental education level was negatively associated with community violence exposure, and positively associated with FSIQ (Table 1). Compared to participants who paid full price for lunch, participants who received free/reduced lunch on average had more community violence exposure ($t_{44} = 2.38$, $p = .02$, 95% CI [.68, 8.10], Hedges' $g = 0.50$; Levene's test indicated unequal variances, $F_{1,63} = 7.36$, $p = .009$, so degrees of freedom were adjusted from 63 to 44) and lower FSIQs ($t_{58} = -2.98$, $p = .004$, 95% CI [−16.41, −3.21], Hedges' $g = 0.91$).

3.2 | Cognitive ability

FSIQ score was negatively associated with community violence exposure (Table 1), and this relationship remained significant when controlling for SES, age, and gender (one-tailed, $p = .04$; Figure 1).

TABLE 1 Correlation coefficients with 95% confidence intervals for the relationships between community violence exposure, IQ, and SES

Variable		1	2
1.	Community violence	–	
2.	Parental education (years)	−.438** [−.62, −.22]	
3.	FSIQ	−.338** [−.55, −.09]	.458** [.23, .64]

Note. Bivariate correlations are presented. FSIQ data were missing for 5 participants. Correlations for variable 3 are based on 60 subjects, while correlations between variables 1 and 2 are based on 65 subjects.
**$p < .01$.

3.3 | Neuroimaging

Controlling for SES (parental education and free/reduced lunch), gender, age, ethnic group, and whole-brain gray matter volume, whole-brain regression analysis yielded a significant negative association between community violence exposure and gray matter volume in the left anterior cingulate cortex (ACC) and the left inferior frontal gyrus (IFG; see Figure 2a and Table 2). No region showed a significant positive association between gray matter volume and community violence exposure. For visualization purposes, Figure 2b shows the average gray matter volume of the clusters plotted against community violence

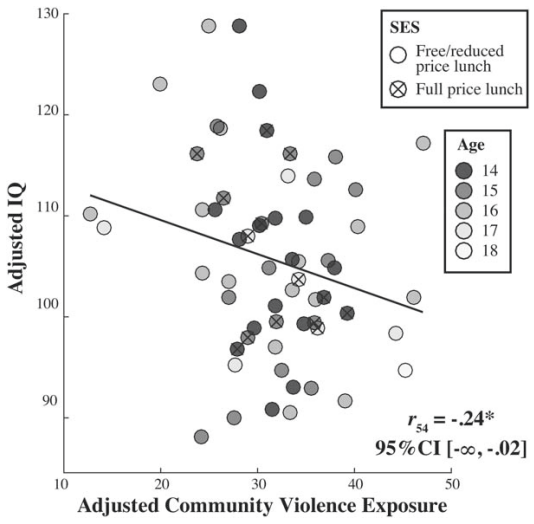

FIGURE 1 Association between community violence exposure and FSIQ. A scatter plot with the best-fitting regression line illustrates the negative association between FSIQ and community violence exposure, controlling for SES (parental education level and eligibility for free/reduced school lunch), age, and gender. FSIQ and community violence exposure values are adjusted for parental education level, eligibility for free/reduced school lunch, age, and gender. The correlation coefficient is reported, along with the lower bound one-tailed 95% confidence interval in brackets. For illustration purposes, participants are labeled by school lunch status and age in years. *$p < .05$, one-tailed

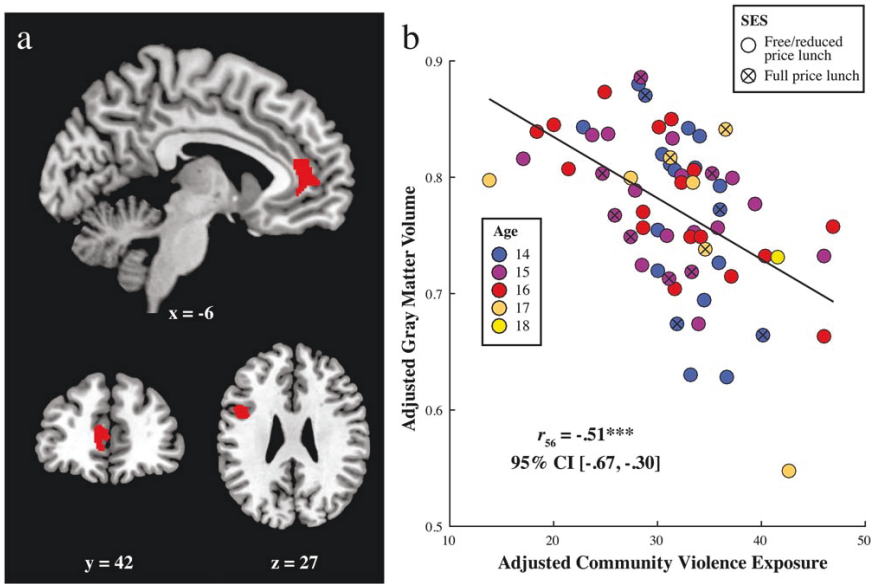

FIGURE 2 Association between community violence exposure and gray matter volume. (a) The brain image displays negative correlations between community violence exposure and gray matter volume, controlling for SES (parental education level and free/reduced lunch status), total gray matter volume, age, gender, and ethnicity, in the left anterior cingulate cortex (ACC, Montreal Neurological Institute coordinates: $x = -10.5$, $y = 45$, $z = 7.5$; $k = 471$) and left inferior frontal gyrus (IFG; Montreal Neurological Institute coordinates: $x = -49.5$, $y = 10.5$, $z = 27$; $k = 325$). Clusters that exceeded a voxel level threshold of $p < .005$ and a cluster size of $k > 205$ (expected voxels per cluster and nonisotropic smoothness corrected) are displayed. (b) A scatter plot with the best-fitting regression line reillustrates the association between community violence exposure and average gray matter volume across the clusters depicted in (a). Gray matter and community violence exposure values are adjusted for parental education level, eligibility for free/reduced school lunch, total gray matter, age, gender, and ethnicity. The correlation coefficient is reported, along with the 95% confidence interval in brackets. For illustration purposes, participants are labeled by school lunch status and age in years. ***$p < .001$

exposure. Supporting Information, Figure S1 presents scatterplots for each region separately.

ROI analyses revealed no effects in the hippocampus ($r_{56} = 0.12$, $p = .38$ 95% CI [−.15, .37]) or amygdala ($r_{56} = -.03$ $p = .80$, 95% CI [−.29, .23]). As in the whole-brain analysis, we controlled for SES, total gray matter volume, ethnicity, age, and gender. We also tested whether FSIQ was associated with gray matter volume and found no significant results in whole-brain or ROI analyses.

For completeness, we repeated the analyses of violence exposure on gray matter volume controlling for FSIQ and the results were essentially unchanged. We tested for violence exposure by SES interactions on FSIQ and on gray matter volume for the clusters identified in the whole-brain analysis, and for the amygdala and hippocampus, and found none.

TABLE 2 Brain regions showing significant relationships to violence exposure

Region	Side	BA	Voxels	*x*	*y*	*z*	*r*
ACC	Left	32	445	−10	45	7	−.41*** [−.59, −.18]
IFG	Left	44	325	−48	9	27	−.47*** [−.64, −.26]

Note. Abbreviations: ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; BA = Brodmann's Area.
Correlations between community violence exposure and gray matter volume from clusters identified as significant in the whole-brain analysis. Results are presented controlling for parental education level, eligibility for free/reduced school lunch, total gray matter volume, age, gender, and ethnicity, with 95% confidence intervals in brackets. Clusters that exceeded a voxel-level threshold of $p < .005$ and a cluster size of $k > 205$ (expected voxels per cluster and nonisotropic smoothness corrected) are reported. Peak coordinates are given in Montreal Neurological Institute (MNI) space.
***$p < .001$.

4 | DISCUSSION

Community violence exposure was associated with lower IQ and smaller gray matter volume in left ACC and left IFG, even after controlling for SES (parental education levels and free/reduced school lunch status, a measure of household income relative to needs). Our findings fit with literature showing that community violence exposure is associated with worse cognitive outcomes (Delaney-Black et al., 2002; Ratner et al., 2006; Sharkey, 2010). Notably, our finding in the ACC overlaps with results from previous studies of soldiers deployed to war (Butler et al., 2017) and of a PTSD meta-analysis (Kühn & Gallinat, 2013). Figure 3 provides the graphical overlay of the current results with results from a study of military deployment (Butler et al., 2017) and from a PTSD meta-analysis (Kühn & Gallinat, 2013).

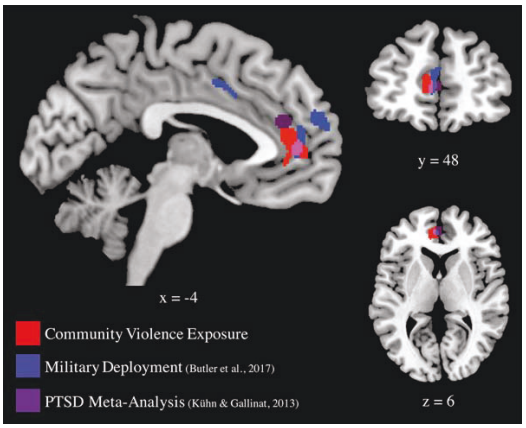

FIGURE 3 Community violence exposure, military deployment, and PTSD. Brain images display the negative correlations between community violence exposure and gray matter volume from the current study in red; results from a previous neuroimaging study showing a negative correlation between military deployment and gray matter volume (Butler et al., 2017) in blue; and results from a PTSD meta-analysis (Kühn & Gallinat, 2013) in magenta. Note the overlapping results in anterior cingulate cortex

The ACC is part of the autonomic regulatory system and, as a centrally connected cortical "hub," is involved in multiple processes that integrate emotion and cognition, including pain processing, arousal, modulation of memory and internal emotional responses (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995), and processing social emotions (Immordino-Yang, McColl, Damasio, & Damasio, 2009). The ACC has been previously implicated in the neurocircuitry of PTSD (Rauch, Shin, & Phelps, 2006), and smaller volumes in the ACC have been linked to depression (Drevets, Savitz, & Trimble, 2008; Frodl et al., 2008; Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013) and to PTSD (Kühn & Gallinat, 2013). The left IFG is involved in cognitive control and language production, and damage to the left IFG has been associated with cognitive and emotional impairments including reductions in emotional empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). In addition, activation of the left IFG has been associated with cognitive control and response inhibition in children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002).

As adolescence is a sensitive period in brain development, this age group may be particularly vulnerable to the effect of stress on the brain and cognitive functions. Though loss of gray matter volume is a normal part of brain maturation in adolescence (Gogtay et al., 2004), a longer trajectory of maturation, that is, slower loss of gray matter, has been associated with higher cognitive function (Shaw et al., 2006), while faster maturation, specifically myelination of white matter, has been associated with increased risk taking and higher rates of alcohol use disorder (Berns, Moore, & Capra, 2009; De Bellis et al., 2008). In particular, it has been hypothesized that a prolonged phase of prefrontal maturation may provide an extended period for the development of high-level cognitive functions (Shaw et al., 2006), although there is some debate in the literature regarding this interpretation (Lu & Sowell, 2009), with some studies linking thinner cortex with higher intelligence in childhood and adolescence (e.g., Schnack et al., 2015). Our findings suggest that violence exposure during adolescence may be associated with less gray matter volume in certain frontal regions, though we cannot discern whether this finding is due to stress-related loss, or to another process, such as accelerated maturation. Future work should investigate whether violence-exposure-related gray matter loss prematurely attenuates the period of adolescent neural plasticity thought to be important for the development of higher executive and cognitive functions. Although no relationship between IQ and gray matter volume was found in this study, possibly due to the cross-sectional design, the age range of the sample or the two-year delay between neuroimaging and IQ testing, our finding that violence exposure correlates with lower IQ would accord with this interpretation.

This study purposefully excluded individuals with current or previous psychiatric disorders and engaged participants and their parents in detailed private interviews about their emotional wellbeing and social relationships; however, there was no measure of symptoms of psychiatric disorders at a subclinical level. As such, we do not know whether smaller gray matter volumes or higher community violence exposure correlate with increased, but subclinical, psychological symptoms in the current sample. In addition, although participants reported no current or historic psychiatric disorders, participants did not complete a full clinical screening and it is possible that some individuals had an undiagnosed clinical disorder. It is also possible that these youths' family relationships, or some other factor, effectively buffered them. Previous studies have shown that community violence exposure is associated with increased risk for psychiatric illness (McDonald & Richmond, 2008), but also that parental warmth is protective (Chen, Miller, Kobor & Cole, 2011). Stress exposure has previously been shown to correlate with smaller PFC gray matter volumes and increased PTSD symptoms in a subclinical population (Butler et al., 2017). Future work should investigate any link to subtle psychological symptoms associated with gray matter reductions in this age group.

In this study, we were particularly interested in demonstrating that community violence correlates with smaller gray matter volume and lower IQ in healthy, nondelinquent adolescents who did not perpetrate violence. Although structural deficits in the ACC have previously been observed among youth with antisocial or aggressive behavior (Ducharme et al., 2011; Gavita, Capris, Bolno & David, 2012; Hyatt, Haney-Caron & Stevens, 2012), adolescents engaging in antisocial behavior were excluded. It is possible the inclusion and exclusion criteria lead to a truncation of the distribution, and that some individuals with community violence exposure and smaller frontal gray matter volume may also engage in antisocial or delinquent behavior. Further work may seek to replicate or extend the current findings in delinquent populations, and to test the possibility that violence exposure may produce subtle antisocial tendencies even in healthy, high-functioning adolescents like those in our sample.

In addition, the current sample was recruited from low-SES neighborhoods in Los Angeles, but some individuals' families were experiencing more severe financial difficulty than others'. We note that the portion of the sample reporting the highest levels of violence exposure

was in this lower SES group, which also tended to be disproportionately Latino (reflecting the lower SES status of Latinos compared to Asians in these neighborhoods). These findings leave open the future question of whether there are differences in the impact of violence by race/ethnic background, or by socioeconomic circumstances. Previous work suggests that under conditions of economic disadvantage, environmental conditions have greater impact on IQ scores (Tucker-Drob & Bates, 2015; Turkheimer, Harden, D'Onofrio, & Gottesman, 2009). Future research could begin to tease apart how the effects of violence exposure may disproportionately impact youth depending on their ethnic background, cultural orientation, and associated differences in demographics and access to resources.

No correlation was observed between violence exposure and hippocampal or amygdala volume at the whole brain or ROI level. Preliminary evidence suggests that abuse during childhood and early adolescence is associated with reduced hippocampal and amygdala volume while stress during middle adolescence is associated with reduced frontal cortical volume (Andersen et al., 2008; Lupien et al., 2009), although one should also note that hippocampal deficits are not consistently observed in pediatric populations (Bick & Nelson, 2016; De Bellis, Hall, Boring, Frustaci, & Moritz, 2001; Woon & Hedges, 2008). Alternatively, it is possible that due to the current sample size, we were underpowered to detect smaller effects. We note that imposing a slightly lower voxel-level height threshold before stringently controlling for cluster extent and type-1 error rate produces additional findings in the dorsomedial and ventromedial prefrontal cortices, and right inferior frontal gyrus in our sample (Supporting Information, Figure S2). These regions should be examined in future studies.

It has previously been shown that stress-related changes in brain structure are reversible and can be altered by psychological and behavioral interventions (McEwen, 2007). Therefore, although we find that community violence exposure has negative effects at the neural and cognitive levels, it is unclear whether and how these effects may be reversed or buffered. Additional work on possible interventions and supports that school and community service programs could provide against the long-term effects of violence exposure on the brain, and on cognitive and psychiatric outcomes, is required.

A potential limitation of this research is that individuals were assessed cross-sectionally and that the reported associations between brain structure, community violence, and psychological symptoms represent interpersonal differences whose etiology has not been observed. Therefore, although we may hypothesize based on animal models that increases in stress exposure lead to decreases in gray matter volume (Lupien et al., 2009; Sapolsky et al., 1985; Selye, 1936), it is also possible that lower gray matter volume and lower cognition were present prior to community violence exposure, or even predisposed youths to exposure. For example, though no neural data were included, Danese et al. (2017) demonstrated that cognitive deficits in victimized adolescents were nonsignificant after controlling for SES, parents' IQ, and the adolescents' cognitive functioning in childhood. Though our neural study controlled for participants' adolescent IQ and for SES, including parental education (which is a significant predictor of children's IQ; e.g., Neiss & Rowe, 2000), we did not assess childhood cognitive functioning or neural structure in our sample. Longitudinal data are needed to learn more about the temporal dynamics and possible reciprocal causal effects of early interpersonal differences in neural development, cognition, and context on individuals' later vulnerability to violence exposure. In addition, the relationship between stress and brain volume has previously been shown to be mediated by alterations in stress hormones, such as cortisol (Lupien et al., 2009; Sapolsky, 1999; Sapolsky, Krey, & McEwen, 1986). However, no hormonal data were collected for the current sample. Future work that incorporates hormonal or other biological measures of long-term stress exposure is required.

This is the first structural MRI study to provide evidence of a relationship between community violence exposure and adolescent brain morphology. Previous studies have linked community violence exposure to increases in psychological symptoms and decreases in attention and cognition. The current results provide first evidence that regions involved in cognition and affect, and that are implicated in PTSD, appear to be selectively affected by exposure to community violence, even in healthy, nondelinquent adolescents who do not perpetrate violence and who have not been direct victims. The present findings serve to underscore the need for greater understanding of how decreases in frontal gray matter volume may contribute to the functional deficits and cognitive effects observed in this and previous studies. These findings emphasize the need for greater recognition of the impact of community violence on adolescents' brain, cognition, and affect and the urgency and importance of greater preventative measures and targeted interventions.

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DECLARATION OF CONFLICTING INTERESTS

All authors report no biomedical financial interests or potential conflicts of interest.

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AUTHOR CONTRIBUTIONS

MHI-Y and X-FY designed and carried out the experiment. OB, MHI-Y, X-FY, CL, and SK analyzed the data and drafted the manuscript. All authors made final comments on the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Paper III

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ORIGINAL ARTICLE

Cognitive Reappraisal and Expressive Suppression of Negative Emotion in Combat-Related Posttraumatic Stress Disorder: A Functional MRI Study

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Abstract
Difficulties in the regulation of emotion are hypothesized to play a key role in the development and maintenance of posttraumatic stress disorder (PTSD). The current study used functional magnetic resonance imaging (fMRI) to assess neural activity during task preparation and image presentation during different emotion regulation strategies, cognitive reappraisal and expressive suppression, in PTSD. Patients with combat-related PTSD (n = 18) and combat-exposed controls (n = 27) were instructed to feel, reappraise or suppress their emotional response prior to viewing combat-related images during fMRI, while also providing arousal ratings. In the reappraise condition, patients showed lower medial prefrontal neural activity during task preparation and higher prefrontal neural activity during image presentation, compared with controls. No difference in neural activity was observed between the groups during the feel or suppress conditions, although patients rated images as more arousing than controls across all three conditions. By distinguishing between preparation and active regulation, and between reappraisal and suppression, the current findings reveal greater complexity regarding the dynamics of emotion regulation in PTSD and have implications for our understanding of the etiology and treatment of PTSD.

Keywords PTSD · fMRI · Emotion regulation · Stress · Combat · Military

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder, which develops following exposure to extreme stress or trauma. Trauma-related symptoms, including hyperarousal, avoidance and intrusive memories, are often experienced in the period immediately following trauma exposure (McFarlane 2000). In the majority of cases these symptoms resolve in the first month following exposure, however a subset of individuals will go on to develop the

Oisin Butler and Gerd Willmund have contributed equally to the work.

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persistent symptoms that characterize PTSD (Kessler 1995). One reason for the failure of symptoms to resolve over time may be the use of emotion regulation strategies that aim to suppress rather than modify an emotional response, when confronted with negative emotions (Cisler and Olatunji 2012; Gross 1998; Moore et al. 2008; Tull et al. 2007).

Gross's highly influential process model of emotion regulation distinguishes regulation strategies by the point at which they occur during an unfolding emotional response. At the broadest level, strategies can be divided into early (antecedent-focused) and late (response-focused) (Gross 1998, 2002). Early strategies aim to modify an emotional response before it occurs, such as through reinterpreting the meaning or context of a stimulus—situation-focused cognitive reappraisal—or by modifying one's perspective—self-focused cognitive reappraisal (Ochsner et al. 2004; Willroth and Hilimire 2016). For example, when faced with a challenging situation, a medical professional may adopt a professional distance to perceive it in a detached and objective manner rather than a personal or emotional one (Doulougeri et al. 2016; Ochsner et al. 2004; Shapiro 2013). In contrast, late strategies attempt to inhibit an emotional response once it has already occurred, for example, by suppressing any outward expression of emotion. Late strategies have been shown to be less effective than early strategies in regulating experienced emotion (Gross 1998).

In PTSD populations, difficulties with emotion regulation were found to be significantly associated with PTSD symptom severity and to partially mediate the relationship between PTSD and related comorbidities (Klemanski et al. 2012). PTSD symptoms have been associated with greater spontaneous use of suppression and less use of reappraisal (Shepherd and Wild 2014), and shifting from suppression-(late) to reappraisal-based (early) emotion regulation strategies has been associated with improvements in treatment outcomes (Price et al. 2006). In addition, therapeutic interventions such as cognitive behavior therapy (CBT) aim to promote emotional regulation self-efficacy, training clients to change their emotions by changing their thoughts through cognitive restructuring (Beck 2011).

At the neural level, cognitive reappraisal and expressive suppression have been shown to be both functionally and temporally distinct. Previous work in healthy individuals (Goldin et al. 2008) has demonstrated that during emotion regulation, patterns of neural activity differ between reappraisal and suppression and change over time, with reappraisal showing a pattern of high initial medial prefrontal neural activity which then decreases over time and suppression showing low initial medial prefrontal neural activity which then increases. At a functional level, the medial prefrontal cortex is involved in multiple processes relevant to emotion regulation, including emotional processing and modulation of the fear response (Diekhof et al. 2011; Etkin et al. 2011; Milad et al. 2007a, b; Northoff et al. 2006). At a structural level, regions within the medial prefrontal cortex show strong connections to the limbic system, including the amygdala (Bush et al. 2000; Devinsky et al. 1995). Goldin et al. conclude that the early activation of prefrontal control regions during reappraisal leads to the effective down-regulation of amygdala and insular reactivity, accompanied by successful regulation of the emotional response and a reduced need for continued cognitive control. Conversely, during suppression, later activation of prefrontal control regions seemingly fails to inhibit the emotional response, leading to a need for sustained activity in these regions and no decrease in amygdala and insular activity.

PTSD patients have previously demonstrated less prefrontal neural activity than controls in response to threat-related stimuli, and this is thought to play a key role in the development and maintenance of PTSD symptoms (Rauch et al. 2006; Shin et al. 2006). Lower prefrontal neural activity has also been observed during the down-regulation of negative emotion in PTSD, in populations as diverse as female victims of sexual violence (New et al. 2009), male combat veterans (Rabinak et al. 2014) and male and female motor vehicle accident victims (Xiong et al. 2013). The above studies did not contrast different types of down-regulation, such as expressive suppression and cognitive reappraisal. However, in a study by Shepherd and Wild (Shepherd and Wild 2014), PTSD patients and trauma-exposed controls were instructed to feel, maintain or decrease their emotional response to negative and neutral images. PTSD symptoms were associated with greater spontaneous use of suppression and less use of reappraisal (Shepherd and Wild 2014). In addition, previous neuroimaging work in PTSD has not distinguished between task preparation and image presentation. It is therefore unclear whether and how neural activity alters during an unfolding emotional response in individuals with PTSD, and whether patterns of change differ between groups in during suppression, as both groups can employ suppression when instructed.

In the current study, we investigate neural and behavioral differences between combat-related PTSD patients and combat-exposed controls during an emotion regulation task. In line with Gross's process model of emotion regulation, we distinguish between cognitive reappraisal and expressive suppression. In addition, previous work has demonstrated that patterns of neural activity not only differ between reappraisal and suppression, but also change over time (Goldin et al. 2008, 2009), and that physiological and behavioral changes are observable during preparation for emotion regulation (Gross 1998). Gross and colleagues propose that when individuals are aware that they will soon be required to manage their emotions, they "appear to steel themselves", and that physiological and behavioural changes are indicative of an individual's efforts to prepare themselves (1998). As

such, we also distinguish between preparatory neural activity, during the instruction phase, and active emotion regulation, during the image presentation phase, a distinction that has not previously been made in neuroimaging research on PTSD.

We recruited patients with combat-related PTSD and combat-exposed individuals without psychopathology, and employed a mixed design to compare the effects of cognitive reappraisal and expressive suppression on subjective arousal and neural activity in individuals with and without PTSD. Combat-related images were used to generate a powerful trauma-related negative affective state. We hypothesize that during emotional regulation, patients and controls will differ at both a behavioral and neural level. On the basis of previous literature, one may postulate on a number of potential neural patterns that PTSD patients may demonstrate. Based on neuroimaging work in PTSD, one may expect that prefrontal neural activity will be lower in PTSD patients than controls during all stages and for all forms of emotion regulation (New et al. 2009; Rabinak et al. 2014; Rauch et al. 2006; Xiong et al. 2013). Alternatively, if PTSD is particularly associated with the use of suppression (Shepherd and Wild 2014), then one may expect that when instructed to use reappraisal, PTSD patients will rather demonstrate a pattern similar to suppression in healthy controls, of lower initial prefrontal neural activity which then increases (Goldin et al. 2008). In this case, one would not expect to observe a difference between patients and controls. We aim to clarify whether during cognitive reappraisal, PTSD patients show reduced neural activity across both task preparation and stimulus presentation, or if they present a pattern similar to that of expressive suppression in healthy controls, with lower preparatory neural activity followed by sustained activity during stimulus presentation. At the behavioral level, we hypothesize that PTSD patients will be less effective in down-regulating emotion and will report higher subjective arousal ratings than controls during cognitive reappraisal and expressive suppression.

Methods and Materials

Participants

Eighteen soldiers with combat-related PTSD, prior to onset of therapy, and 27 combat-exposed soldiers without mental illness were recruited from the German Armed Forces. Participants were screened for inclusion and exclusion criteria. Inclusion criteria: all participants were male, had been previously deployed overseas to areas of conflict, and had experienced trauma within the last 2 years, as assessed by the Mental Health Advisory Team Combat Experiences Scale. Clinical psychologists interviewed participants, and for the patient group a diagnosis of PTSD was made using ICD 10 criteria. Exclusion criteria: no participants had MRI contraindications or a history of concussion or traumatic brain imagery, none were using psychotropic medication or had current or previous comorbid Axis II psychiatric disorders (American Psychiatric Association 2000). The mean age of the patient group was 28.3 years ($SD = 6.4$, ranging between 23 and 52 years) and the mean age of the control group was 32.7 years ($SD = 5.9$, ranging between 23 and 47 years). Because the patient group was significantly younger than the control group [$t(43) = 2.387$, $p < 0.05$], in the subsequent reported neuroimaging analyses, age was included as a covariate of no interest, although repeating the neuroimaging analyses without including age did not change the results.

All participants had completed secondary education, and the proportion of patients (12 of 18) and controls (21 of 27) who had completed additional vocational training was not significantly different [$X^2(1, N = 45) = 2.143$, $p = 0.143$].

The protocol was approved by the ethics committee of Charité University Clinic, Berlin, Germany, and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

Questionnaires

Prior to neuroimaging, all participants completed a number of questionnaires assessing psychological symptoms and experiences during deployment. Participants completed German versions of the following self-report questionnaires: the Post-traumatic Diagnostic Scale (PDS) (Foa et al. 1997), the Posttraumatic Cognitions Inventory (PTCI) (Foa et al. 1999), the Interpretation of PTSD Symptoms Inventory (IPSI) (Clohessy and Ehlers 1999) and a 33-item questionnaire measuring frequency of combat-related events based on the list of the Mental Health Advisory Team Combat Experiences Scale (MHAT-CES) (Hoge et al. 2004; Mental Health Advisory Team 2006). Independent samples *t* tests were conducted on questionnaire data. Patients scored significantly higher than controls on PTSD questionnaires (PDS, PTCI & IPSI) but not on combat experiences (MHAT-CES) (see Table 1). MHAT-CES data was missing for four patients.

Scanning Procedure

Magnetic resonance images were acquired using a 3 T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) and a 12-channel radiofrequency head coil. Structural images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI protocol (http://www.adni-info.org; TR = 2500 ms; TE = 4.77 ms; TI = 1100 ms, acquisition matrix = 256 × 256 × 176, flip

Table 1 Results for PTSD and combat-exposure questionnaires

Questionnaire	Patients		Controls		*t* test	Cohen's D
	M	SD	M	SD		
PDS	36.28	10.65	4.11	4.1	14.26***	3.99
PTCI	125.06	24.45	46.70	13.57	13.81***	3.96
IPSI	4.74	1.38	1.85	0.47	10.09***	2.80
MHAT-CES	1.87[a]	0.94	1.72	1.23	*0.41*	0.14

M mean, *SD* standard deviation, *PDS* Posttraumatic Diagnostic Scale, *PTCI* Posttraumatic Cognitions Inventory, *IPSI* Interpretation of PTSD Symptoms Inventory, *MHAT-CES* Mental Health Advisory Team Combat Experiences Scale

***$p < 0.001$

[a]MHAT data was missing for four patients

angle = 7°; 1 × 1 × 1 mm^3 voxel size). Whole-brain functional images were acquired using a T2*-weighted echo-planar-imaging (EPI) sequence sensitive to *bold* contrast (TR = 2000 ms, TE = 30 ms, image matrix = 72 × 72, FOV = 216 mm, flip angle = 80°, slice thickness = 3.0 mm, distance factor = 20%, slice order = interleaved, voxel size 3 × 3 × 3 mm^3, 36 axial slices).

Image Stimuli

Sixty combat images were selected from a larger battery of genuine war photographs provided by the German Armed Forces, taken by soldiers during active duty, mainly in Afghanistan. Combat images were selected as we consider these images to be more salient to our participants than negative images from other potential sources, for example the International Affective Picture System (IAPS) (Lang et al. 2008). Affective valence and arousal of the images were assessed by the experimenters, and images with unpleasant valence and medium arousal were selected. Examples included photos of destroyed vehicles, explosions and soldiers under enemy fire. Images showing explicit scenes of death or injury were excluded to reduce the likelihood of images triggering a flashback in the patient population.

Emotional Regulation Instructions

Prior to magnetic resonance imaging (MRI), participants were instructed in cognitive reappraisal and expressive suppression strategies (see Supplemental Material S1 for original instructions in German and Supplemental Material S2 for English translation). In the feel condition, participants were instructed to allow the image to trigger an emotional response and to experience this emotional response. For reappraisal, participants were instructed to think objectively while viewing the images in order to decrease emotional reactivity. They were to adopt the perspective of a professional performing a task requiring high concentration and try to perceive the stimuli objectively, rather than emotionally. In the suppress condition, participants were instructed to suppress any outward signs of emotion, so that an external observer would be unable to detect what the participant was experiencing subjectively. In the current study, we compare PTSD patients prior to onset of therapy to controls, and are interested in assessing neural and behavioral differences in their current ability to employ different emotion regulation strategies, rather than the ability to develop these techniques with training. As such, we provide instructions including a specific example, but not additional training in emotion regulation techniques. The instructions and approach that we employ are similar to those used in previous studies (Goldin et al. 2008, 2009; Gross 1998; Gross and Levenson 1997; McRae et al. 2008; Ochsner et al. 2002).

Experimental Task

Sixty combat-related images were presented using adjustable goggles and Presentation® software (Version 0.70, http://www.neurobs.com). We employed an event-related design, with the twenty trails per condition (feel, reappraise and suppress) randomly interspersed, rather than presented in a continuous block. In addition, condition-image combinations were counterbalanced across participants to ensure that images were not consistently paired with the same emotion regulation condition. A variable jitter interval of 0–1.5 s (varied in steps of 500 ms) was inserted before the instruction phase.

Prior to each image, there was a preparation phase, in which the instruction *feel* (*Fühlen*), *reappraise* (*Distanzieren*) or *suppress* (*Unterdrücken*) was presented for 1 s. Following this there was a presentation phase, in which the target image was then presented for 10 s. Participants were then asked to rate on a scale 1–4, "How much were you affected by this image?" (*Wie sehr hat Sie dieses Bild bewegt?*), with 1 indicating not affected and 4 indicting strongly affected. Participants responded using a 4-button response box in their right hand, and the scale was randomly presented in the order 1–4 or 4–1 to avoid movement

preparation. The duration of the scale presentation was response-dependent. An 8-s fixation cross was then presented (see Fig. 1).

Functional MRI Statistical Analysis

The fMRI data were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). The first four volumes of all Echo Planar Imaging (EPI) series were excluded from the analysis to allow the magnetization to approach a dynamic equilibrium. Data processing started with slice time correction and realignment of the EPI datasets. A mean image for all EPI volumes was created, to which individual volumes were spatially realigned by means of rigid body transformations. The structural image was co-registered with the mean image of the EPI series. Then the structural image was normalized to the Montreal Neurological Institute (MNI) space using the ICBM152 template (Mazziotta et al. 2001), and the normalization parameters were applied to the EPI images to ensure an anatomically informed normalization. To correct for head movement, participants showing head motion above 3 mm of maximal translation (in any direction of x, y or z) and 3.0° of maximal rotation throughout the course of scanning would have been excluded. No participants showed head movements that exceeded these boundaries. A commonly applied filter of 8 mm full-width at half maximum (FWHM) was used. Low-frequency drifts in the time domain were removed by modeling the time series for each voxel by a set of discrete cosine functions, to which a cut-off of 128 s was applied.

The statistical analyses were performed using the general linear model (GLM). We modeled the instruction as an event to capture brain activity related to the preparatory phase, and modeled the target as a block (duration 10 s) to capture actual emotion regulation during image presentation. These vectors were convolved with a canonical hemodynamic response function (HRF) and its temporal derivatives to form regressors in a design matrix. The parameters of the ensuing GLM were estimated using the SPM8 standard specifications and used to form whole brain contrasts, comparing each condition with baseline (fixation cross) to test for main effects between conditions resulting in six separate linear contrast images (preparatory phase: feel-baseline, reappraise-baseline, suppress-baseline; image presentation: feel-baseline, reappraise-baseline, suppress-baseline). Separately for both groups, statistical information from all contrasts can be found in the supplemental material (see Supplemental Material S3). Following this, each emotion regulation condition was contrasted with the feel condition, resulting in four separate contrasts (preparatory phase: reappraise-feel, suppress-feel, image presentation: reappraise-feel, suppress-feel). The resulting contrast images were then entered into a series of two sample *t* tests at the second (between-subject) level, where we compared the two groups. A significant effect was reported when the results met a peak-level threshold of $p < 0.001$ and a cluster-level threshold of $p < 0.05$ in SPM, and when the size of the cluster was greater than the Monte Carlo simulation determined minimum cluster size above which the probability of type I error was < 0.05, using the 3dClustSim method,

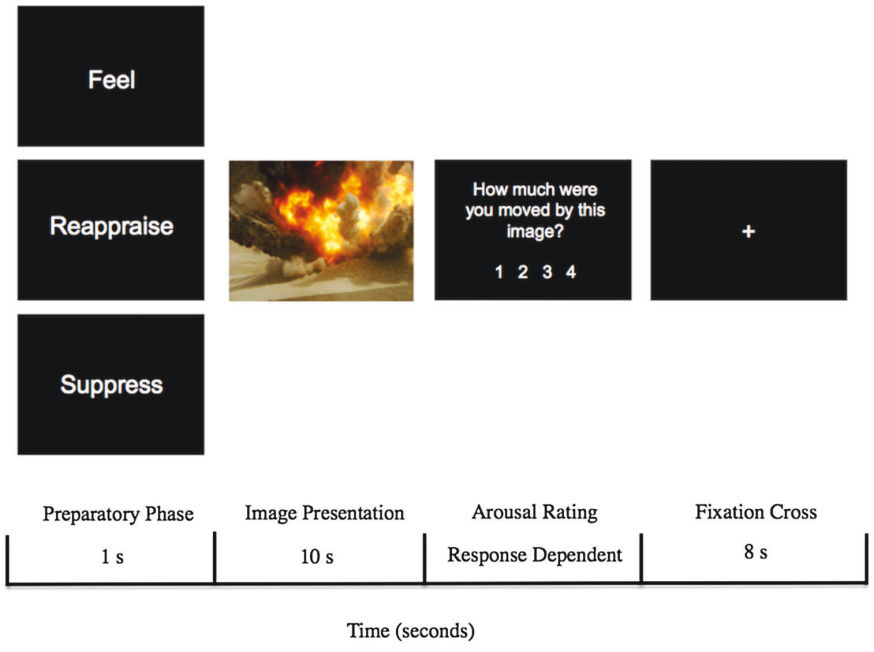

Fig. 1 Experimental design for a single trial. The experiment consisted of 60 trials with 60 unique combat-related images. 20 trials of each condition (feel, reappraise and suppress) were randomly interspersed in an event related design. A single trial consisted of a variable jitter interval of 0–1.5 s (varied in steps of 500 ms), a 1 s instruction to either feel, reappraise or suppress, 10 s image presentation, "How much were you moved by this image?" (1–4) was presented until the participant made a response, and an 8-s fixation cross

implemented in AFNI version 16.3.07 ($\alpha < 0.05$, $p < 0.001$, FWHM $13.17 \times 12.93 \times 12.72$, two-tailed) $k = 56$ voxels (Cox 1996; Cox et al. 2017). Monte Carlo simulation is a commonly used and widely accepted cluster correction method for SPM analyses (Cox et al. 2017; Ward 2000). The FWHM smoothness estimate was calculated directly from the data, as the average of the individual smoothness estimates. Due to the novel nature of this study, we also tested a more lenient threshold of ($\alpha < 0.10$, $p < 0.001$, FWHM $13.17 \times 12.93 \times 12.72$, two-tailed) $k = 45$ voxels, and report the single cluster that met this threshold, although due to the more lenient threshold this cluster should be interpreted with caution. For display purposes the resulting SPMs were thresholded at $p < 0.001$ (uncorrected). In addition, for information purposes we also report exploratory analysis at the lenient voxel level threshold of $p < 0.005$, and cluster corrected at $k = 56$ voxels (see Supplemental Material S4).

Rather than adopting a time-series analysis approach such as the one used by Goldin et al. (2008), we analyzed the image presentation phase as a single block. In the study by Goldin, images were presented for 15 s and the task was completed in three 9-min runs, while in the current study images were presented for 10 s, and the task was completed in 2 to 10-min runs. We chose a shorter image presentation duration, as we had a higher number of images to present, and we wanted to keep the total task duration down, as we are cognisant that PTSD patients can find MRI scanning unpleasant, due to the close confinement and loud noises. However, given the shorted image presentation, modelling the data using a time series approach is unlikely to produce interpretable results.

Results

Arousal Ratings

A MANOVA was conducted to compare arousal ratings for images for patients and controls. There was a significant group-by-condition interaction $F(1,42) = 5.065$, $p = 0.004$; Wilks's $\Lambda = 0.734$, $\eta^2 = 0.266$. Post-hoc independent and paired-sample t tests were then conducted. Patients found images significantly more arousing than controls for the feel [$t(43) = 2.669$, $p < 0.01$, one-tailed], reappraise [$t(43) = 3.384$, $p < 0.01$, one-tailed] and suppress [$t(43) = 3.683$, $p < 0.001$, one-tailed] conditions (see Table 2). Controls had significantly lower arousal ratings in the reappraisal condition than the feel condition [$t(26) = 1.948$, $p < 0.05$, one-tailed], while patients did not [$t(17) = 0.456$, $p = 0.327$, one-tailed]. Comparing the suppression and feel conditions, neither controls [$t(26) = 1.519$, $p = 0.071$, one-tailed) nor patients [$t(17) = 1.373$, $p = 0.099$, one-tailed] showed a significant difference. In addition, comparing the reappraisal and suppression conditions, neither controls [$t(26) = 0.801$, $p = 0.215$, one-tailed] nor patients [$t(17) = 1.527$, $p = 0.073$, one-tailed] showed a significant difference.

Functional Neuroimaging

Negative Emotion Induction Manipulation Check

To assess if the combat images elicited a neural response we contrasted the feel condition against baseline (fixation cross) for all participants. This contrast revealed higher activity during image presentation in the visual cortex, amygdala/hippocampus and medial orbitofrontal cortex (mOFC) (see Table 3 and Supplemental Material S4 for exploratory analysis). Independent samples t tests were also conducted in SPM and revealed no significant difference between patients and controls in either the task preparation or image presentation phases of the feel condition against baseline.

Preparatory Phase

Next, we turn to the key aim of the study, to investigate neural differences between PTSD patients and controls during the task preparation and image presentation phases of an emotion regulation task. During the preparatory phase, patients showed less activation in the vmPFC and

Table 2 Results for subjective arousal ratings

Condition	Patients		Controls		t test	Cohen's D
	M	SD	M	SD		
Feel	2.40	0.39	1.93	0.66	2.669**	*0.87*
Reappraise	2.43	0.40	1.83	0.67	3.384**	*1.09*
Suppress	2.50	0.38	1.83	0.67	3.683**	*1.23*

Participants rated how much they were affected by images on a scale 1–4, with 1 indicating not affected and 4 indicting strongly affected

M mean, *SD* standard deviation

**$p < 0.01$; ***$p < 0.001$

Table 3 Peak voxels of activated clusters during feel > baseline

Region	BA	MNI coordinates			Laterality	*t* score	*k*
		X	Y	Z			
Patients and controls							
Occipital cortex Extending into amygdala and hippocampus	18	9	− 100	13	R/L	16.95	6185
Medial orbitofrontal cortex	11	0	47	− 20	L	6.01	83

BA Brodmann area, *k* cluster size, *R* right, *L* left

Clusters meeting the minimum cluster size threshold, corresponding to Monte Carlo Simulation using 3dClustSim ($\alpha < 0.05$, $p < 0.001$, k = 56), are reported

Table 4 Peak voxels of activated clusters during reappraisal > feel

Region	BA	MNI coordinates			Laterality	*t* score	*k*
		X	Y	Z			
Preparation							
Controls > patients							
rACC/vmPFC	32	3	35	− 11	R/L	4.39	77
Image presentation							
Patients > controls							
*dACC	24	3	29	13	R/L	5.10	45
Occipital cortex	18	− 15	− 91	1	L	4.36	73

BA Brodmann area, *k* cluster size, *R* right, *L* left, *dACC* dorsal anterior cingulate cortex, *rACC* rostral anterior cingulate cortex, *vmPFC* ventromedial prefrontal cortex

Clusters meeting the minimum cluster size threshold, corresponding to Monte Carlo Simulation using 3dClustSim ($\alpha < 0.05$, $p < 0.001$, k = 56, and $*\alpha < 0.10$, $p < 0.001$, k = 45), are reported

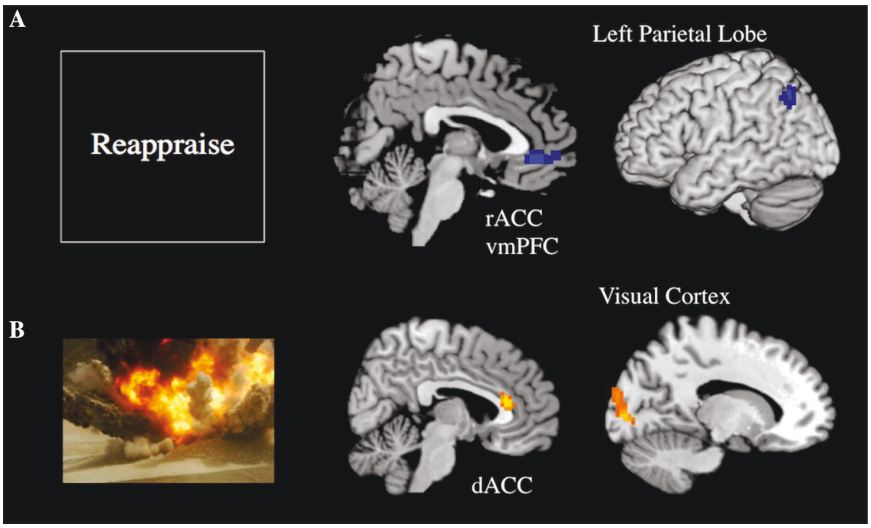

Fig. 2 Brain regions showing a significant group (PTSD patients and controls) difference in the reappraise minus feel condition in blood oxygen level dependent bold signal during **a** preparation and **b** image presentation. Warm colour indicates higher activation, and cold colour indicates lower activation in patients compared with controls during cognitive reappraisal. All clusters significant at $\alpha < 0.05$, $p < 0.001$, k = 56, with the exception of the dACC which was significant at $\alpha < 0.10$, $p < 0.001$, k = 45. *dACC* dorsal anterior cingulate cortex, *rACC* rostral anterior cingulate cortex, *vmPFC* ventromedial prefrontal cortex

left parietal lobe than controls during reappraisal ($\alpha < 0.05$, $p < 0.001$, k = 77) (see Table 4; Fig. 2a, and Supplemental Material S4 for exploratory analysis). No difference was observed in the suppress and feel conditions during the preparatory phase.

Image Presentation

During the image presentation phase, comparing the reappraise and feel conditions, patients showed greater activation in the visual cortex ($\alpha < 0.05$, $p < 0.001$, k = 73) and dACC

($\alpha < 0.10$, $p < 0.001$, k = 45) (see Table 4; Fig. 2b, and Supplemental Material S4 for exploratory analysis) than controls during reappraisal. No difference was observed in the contrast between suppress and feel conditions during the image presentation phase.

Discussion

The goal of this study was to assess differences between combat-PTSD patients and combat-exposed healthy controls during an emotion regulation task, both at a behavioral and neural level. Two emotion regulation strategies, cognitive reappraisal and expressive suppression, were assessed during preparation and image presentation. In the reappraisal condition, controls showed higher prefrontal neural activity than patients during the preparatory phase, while patients showed higher prefrontal neural activity than controls during image presentation. No difference between patients and controls was observed in the suppression condition, either during the preparatory phase or during image presentation.

In the preparatory phase, controls showed higher activation than patients in the vmPFC and rACC, regions that have been previously implicated in affective and cognitive processing, including the regulation of fear expression, memory and emotional processing (Carter et al. 1999; Diekhof et al. 2011; Etkin et al. 2011; Milad et al. 2007a, b), as well as in the neurocircuitry of PTSD (Rauch et al. 2006). The rACC is known to regulate emotional responses and assess the salience of emotional stimuli, and has strong connections to limbic and paralimbic regions including the amygdala (Bush et al. 2000; Devinsky et al. 1995). The vmPFC is known to play a key role in self-referential processing and the extinction of conditioned fear (Milad et al. 2007a; Northoff et al. 2006). Previous work on cognitive reappraisal in healthy controls has demonstrated that early enhanced *bold* responses in the medial prefrontal cortex correlates with reduced late activation of the amygdala (Goldin et al. 2008), and a decrease in self-reported negative experiences. As such, higher activation of these regions during the preparatory phase should lead to more effective down regulation of negative emotion during the image presentation phase. This is reflected in the current results, as controls also reported significantly less arousal than patients.

During image presentation, patients showed higher activity than controls in the dorsal ACC (dACC) and in the visual cortex. The dACC shows strong connections with regions including the dorsolateral prefrontal cortex and supplementary motor areas, and has been implicated in conflict monitoring and response selection (Devinsky et al. 1995). The region observed in this study also corresponds to the anterior mid-cingulate cortex (aMCC) (Rotge et al. 2015), a region shown to be involved in negative affect, (social) pain, and cognitive control (Rotge et al. 2015; Shackman et al. 2011). In addition, the aMCC includes the rostral cingulate zone (RCZ), a region involved in conflict monitoring and facial movement (Picard and Strick 1996, 2001), with links to motor centers responsible for expressing affect and executing goal-directed behavior (Shackman et al. 2011). Greater activation in the visual cortex during image presentation in patients may suggest that controls disengage from the stimuli more than patients. Although not instructed, controls may have spontaneously engaged in attentional deployment, another form of early emotion regulation (Gross 2008). Previous eye-tracking studies have shown that PTSD is related to attentional bias for trauma-related stimuli, accompanied by greater autonomic arousal, compared with trauma-exposed controls (Felmingham et al. 2011; Kimble et al. 2010).

Therefore, patients and controls differ not only on a temporal dimension, but also on a regional, and therewith functional level, suggesting that during the reappraisal condition, patients and controls actually engaged in different strategies at different times. During the reappraisal condition, higher activation in controls in the rACC during the preparation phase may suggest that they implement preparatory affective regulation strategies. Higher activation in patients in the dACC during image presentation may suggest that patients implement more suppression-based strategies, such as control or suppression of motoric responses, later and less effectively, as indexed by higher subjective arousal ratings. In a similar neuroimaging study with healthy controls, higher early activation of prefrontal regions including the mPFC was observed during cognitive reappraisal, while higher late activation in regions including the vmPFC and dACC was observed during expressive suppression (Goldin et al. 2008). We did not observe a difference in neural activity between patients and controls in the suppression condition, either during the preparatory phase or during image presentation. This may indicate that PTSD patients and controls use similar brain regions at similar times when suppressing negative emotion.

We did not observe a difference in amygdala activity between patients and controls in any condition. This may be due to the highly relevant nature of the stimuli, as both groups had been exposed to combat. This is in line with previous neuroimaging studies that have also failed to demonstrate increased amygdala activity in PTSD patients during emotion regulation (New et al. 2009; Rabinak et al. 2014; Xiong et al. 2013), as well as image presentation (Phan et al. 2006) and traumatic reminders (Britton et al. 2005). In future studies, the addition of a non-trauma exposed control group may prove useful in teasing apart differences between trauma exposure per se and PTSD in amygdala reactivity.

One potential limitation of this study is that we did not include a measure of how effectively participants felt they

had implemented each strategy. Previous work in healthy controls that has included a post-task measure to verify that the correct emotion regulation strategy was implemented has shown a compliance rate of 96% (Ochsner et al. 2002). Nevertheless, future work could usefully incorporate a measure of perceived success of strategy implementation to assess how PTSD patients perceive their abilities to down-regulate negative emotion regulation. In addition, the short preparation phase may have resulted in low power and future studies could provide longer preparation times to further disentangle preparation from target presentation.

Another potential limitation is that the patient group was significantly younger than the control group. Previous neuroimaging studies comparing age groups have found age-related differences, however these appear to be more pronounced at the structural level rather than the functional level (Rajah and D'Esposito 2005). In addition, although precise cutoffs vary, studies of age-related differences usually compare younger adults, for example between 18 and 35 years of age, to older adults, 60 years of age and above (Persson and Reuter-Lorenz 2008). However, in the current study, all individuals were in young to middle adulthood, with no individuals in old age. Nevertheless, age was included as a covariate in the neuroimaging analysis, although repeating the analyses without including age did not change the results.

One should also note that the generalizability of the current findings may be limited by both the specific nature and size of the participant groups. Given the relatively small sample size and the unequal subgroup sizes, we may lack sufficient power to detect smaller effects. Future work is needed to replicate the current findings and to explore how these results may extend to non-military and female samples.

In the current study, we analyzed the image presentation phase as a single block, as due to the duration of image presentation modelling the data using a time series approach was unlikely to produce interpretable results. Future studies may consider using a longer image presentation duration, similar to one used by Goldin et al. (2008), to also allow a time-series analysis approach.

The patients in the current study were assessed prior to treatment. Psychotherapies, such as CBT, train individuals to effectively employ emotion regulation techniques (Beck 2011), and one may expect that behavioral and neural correlates of emotion regulation will change following successful therapeutic intervention. Going forward, studies employing a longitudinal design would be useful to assess whether neural correlates of emotion regulation are useful in predicting responsiveness to therapy, and if these patterns change following training and the resolution of symptoms.

Conclusions

In the current study, we distinguish between task preparation and image presentation during two emotion regulation strategies, cognitive reappraisal and expressive suppression. Previous studies have not distinguished between these phases or strategies and show rather a general pattern of reduced neural activity in PTSD patients during emotion regulation. We found however, that patients showed lower neural activity during task preparation, and higher activity during image presentation in the cognitive reappraisal condition, a pattern of activity similar to that previously observed in expressive suppression in healthy controls. In the suppression condition, no difference between groups was observed. The current findings provide greater granularity of detail and reveal greater complexity regarding the neural dynamics of emotion regulation in PTSD than previously described.

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Data Availability The datasets generated and analyzed during the current study are not publicly available as this was not approved by the ethics committee and the participants did not agree to share their data publicly. However, the datasets are available from the corresponding author on reasonable request.

Author Contributions OB and GW contributed equally to this work. OB, GW, TG, PZ, UL, JG and SK contributed to the study design, acquisition and analysis of data and drafting of the manuscript. All co-authors have seen and approve with the contents of the manuscript.

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Compliance with Ethical Standards

Conflict of interest Gerd Willmund and Peter Zimmermann are employed by the German Armed Forces. Their employment had no influence on the study design. All authors declare that they have no conflict of interest.

Ethical Approval The protocol was approved by the ethics committee of Charité University Clinic, Berlin, Germany.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (national and institutional). Informed consent was obtained from all individual subjects participating in the study. All subjects

gave written informed consent in accordance with the Declaration of Helsinki.

Research Involving with Human and Animal Participants No animal studies were carried out by the authors for this article.

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Paper IV

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ORIGINAL RESEARCH

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Hippocampal gray matter increases following multimodal psychological treatment for combat-related post-traumatic stress disorder

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Abstract

Introduction: Smaller hippocampal volumes are one of the most consistent findings in neuroimaging studies of post-traumatic stress disorder (PTSD). However, very few prospective studies have assessed changes in hippocampal gray matter prior to and following therapy for PTSD, and no neuroimaging studies to date have longitudinally assessed military populations.

Methods: A pilot study was conducted, assessing patients with combat-related PTSD with structural MRI. Participants were then assigned either to a treatment group or waiting-list control group. After the treatment group received multimodal psychological therapy for approximately 6 weeks, both groups completed a second neuroimaging assessment.

Results: Region-of-interest analysis was used to measure gray matter volume in the hippocampus and amygdala. There was a group by time interaction; the therapy group (n = 6) showed a significant increase in hippocampal volume and a nonsignificant trend toward an increase in amygdala volume following therapy, while no change was observed in the waiting-list group (n = 9).

Conclusions: This study provides initial evidence for increases in gray matter volume in the hippocampus in response to therapy for combat-related PTSD.

KEYWORDS

adult neurogenesis, post-traumatic stress disorder, psychiatry, stress

1 | INTRODUCTION

Post-traumatic stress disorder (PTSD) is a complex and debilitating psychiatric disorder caused by exposure to traumatic events. Clinically, PTSD is characterized by symptoms of hyperarousal, avoidance, and re-experiencing, including intrusive memories and visual flashbacks of the traumatic event (Gonzalez & Chiodo, 2015). PTSD is unique among psychiatric disorders as the diagnostic criteria require exposure to an identifiable traumatic event.

Military deployment and combat exposure are specific and highly relevant instantiations of repeated stress and trauma. In recent years, military and political conflicts across the globe have increased, resulting in greater numbers of individuals experiencing combat and continuous exposure to extreme stress. Rates of PTSD

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in combat-exposed military populations appear to be consistently higher than in comparable civilian populations (Bandelow et al., 2012; Fear et al., 2010; Kessler et al., 2014; Thomas et al., 2010; Trautmann et al., 2016; Wittchen et al., 2012). In addition, individuals with combat-related PTSD appear to show higher levels of psychopathology (Frueh, Hamner, Cahill, Gold, & Hamlin, 2000) and higher rates of suicide than civilian populations (Kemp & Bosarte, 2012).

At a neural level, trauma and stress exposure have been associated with alterations in the function and structure of the brain. In animal models, chronic stress exposure has been shown to reduce gray matter volume via reductions in dendritic branching and neurogenesis (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen & Morrison, 2013). The hippocampus is particularly vulnerable to the effects of chronic stress, as it has been shown to be highly sensitive to the effect of glucocorticoids (Sapolsky, Krey, & McEwen, 1985; Sapolsky, Uno, Rebert, & Finch, 1990), the main hormone involved in the chronic stress response.

Neuroimaging research on PTSD has reported smaller regional gray matter volumes, including the hippocampus and amygdala (Karl et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Kühn & Gallinat, 2013; Smith, 2005). A key role for these regions in PTSD symptomatology is supported by their well-established roles in memory (Squire, 1992) and the detection of affective or threatening stimuli (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Öhman, 2005). A neurocircuitry model of PTSD proposes that there is a failure to inhibit a fear reaction in response to threat, in part through reduced bottom-up control by the hippocampus on the amygdala (Rauch, Shin, & Phelps, 2006; Shin, Rauch, & Pitman, 2006).

Functionally, the hippocampus is a key region in learning and memory (Squire, 1992). Hippocampal volume has been shown to affect contextual fear conditioning in humans (Pohlack et al., 2012), and smaller hippocampal volume has been associated with increased risk (Gilbertson et al., 2002), longer duration (Apfel et al., 2011; Chao, Yaffe, Samuelson, & Neylan, 2014), and poorer treatment response (Rubin et al., 2016; van Rooij et al., 2015) in PTSD. In animal studies, stress-induced alterations in hippocampal morphology have been linked to increases in anxiety and depression-like behavior (Lagace et al., 2010), and reductions in cognition and memory (Kim, Diamond, Haven, & Blvd, 2002; McEwen & Sapolsky, 1995). Dysfunctions in memory, specifically intrusive memories or flashbacks, are one of the core symptoms of PTSD, while one of the key objectives of therapeutic interventions for PTSD is to reduce the frequency and vividness of these intrusions.

One may postulate that therapeutic interventions for PTSD will increase hippocampal volume. However, there is a paucity of longitudinal or prospective neuroimaging on PTSD. To our knowledge, only two studies to date have longitudinally assessed PTSD patients with structural MRI prior to and following therapy, and no studies to date have assessed combat-related PTSD. In a study by Vermetten, Vythilingam, Southwick, Charney and Bremner (2003), long-term treatment with the antidepressant paroxetine was shown to increase hippocampal volume and improve memory, while in a study by Lindauer et al. (2005), no increase in hippocampal volume was observed following psychotherapy. It remains an open question if and how gray matter changes following psychological therapeutic intervention for combat-related PTSD.

We conducted a pilot longitudinal study to explore changes in gray matter and psychological symptoms following psychological therapy. We recruited soldiers with combat-related PTSD and assessed them with psychological questionnaires and clinical interviews and structural magnetic resonance imaging (MRI) at two time points. Following the first assessment, patients were randomly assigned to either a therapy group or a waiting-list control group. Following completion of therapy, approximately 6 weeks later, both groups of patients were again assessed with psychological questionnaires and structural MRI. Changes in gray matter were assessed using voxel-based morphometry, and gray matter values from the amygdala and hippocampus were extracted using a region-of-interest approach. Regions were selected on a theoretical basis, as alterations in these areas are commonly observed in PTSD populations, and also on a practical basis, as they are discrete and clearly defined anatomical regions.

To our knowledge, this is the first longitudinal study to compare patients with combat-related PTSD before and after therapy to a waiting-list control group. We hypothesized that the therapy group would show both improved symptom scores and increased gray matter following therapy compared with the control group.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty soldiers with combat-related PTSD, prior to onset of therapy, were recruited from the German Armed Forces. All participants were male and had been deployed overseas to areas of conflict. As inclusion criteria, participants were screened by a multidisciplinary team of clinicians, including clinical psychologists and psychiatrists, for the presence of mission-related trauma within the last 2 years and for a current diagnosis of PTSD according to ICD-10 criteria. As exclusion criteria, participants were also screened for current or previous comorbid axis I psychiatric disorders (American Psychiatric Association, 2000) using the Mini-DIPS (Diagnostisches Kurz-Interview bei psychischen Störungen; Margraf, 1994; Sheehan et al., 1998), use of psychotropic medication and MRI contraindications. The local ethics committee of Charité University Clinic, Berlin, Germany, approved the study, and written informed consent was obtained from each participant prior to participation, in line with the Declaration of Helsinki.

Participants were assigned either to a therapy group or a waiting-list control group. The participants in the therapy group underwent psychotherapy between the first and second assessment; participants in the waiting-list control group did not undergo therapy, but had a similar time interval between the two assessments. All participants in the therapy group completed therapy. However, not

all participants completed both assessments, and neuroimaging data from the second assessment were available for six individuals in the therapy group and nine individuals in the control group.

2.2 | Questionnaires

To assess duration of military deployment and experiences during deployment, participants completed the Mental Health Advisory Team's Combat Experiences Scale (MHAT-CES; Hoge et al., 2004; Wittchen, Gloster, Beesdo, Schönfeld, & Perkonigg, 2009), a 33-item questionnaire assessing the type and frequency of combat-related events during military deployment, as well as a study-specific questionnaire that included items on the number and duration of military deployments. MHAT-CES data were available for ten individuals in the therapy group and six individuals in the control group.

To assess psychological symptoms, prior to each neuroimaging session, participants also completed German versions of the following self-report questionnaires; the Brief Symptom Inventory, the Posttraumatic Diagnostic Scale, the Interpretation of PTSD Symptoms Inventory, and the Posttraumatic Cognitions Inventory.

The Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983) is a 53-item self-report questionnaire measuring nine symptom dimensions of psychological distress (e.g., somatization, depression, anxiety, and hostility). Each item was rated on a five-point scale ranging from 0 (not at all) to 4 (extremely), based on the intensity of distress over the past week. For the BSI, we utilize the Global Severity Index (GSI) score, as this is recommended as the single best indicator of current psychological distress levels and is highly reliability over time, with a test–retest coefficient of 0.90 (Derogatis & Melisaratos, 1983). The GSI is calculated by taking the sum of the 53 items.

The Posttraumatic Diagnostic Scale (PDS; Foa, Cashman, Jaycox, & Perry, 1997) is designed to aid in the diagnosis of PTSD and assess symptom severity. As part of the PDS, respondents rated 17 items representing the main symptoms of PTSD experienced in the past 30 days, on a four-point scale. The PDS has both strong internal consistency (Cronbach's $\alpha = 0.92$) and good 3-week test–retest reliability ($\kappa = 0.74$; Foa et al., 1997).

The Interpretation of PTSD Symptoms Inventory (IPSI; Clohessy & Ehlers, 1999) assesses appraisal of PTSD symptomatology over the past month, rated from 1 (totally disagree) to 7 (totally agree) and has good internal consistency (Cronbach's $\alpha = 0.93$; Halligan, Michael, Clark, & Ehlers, 2003).

The Posttraumatic Cognitions Inventory (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999) is a 33-item questionnaire on negative posttrauma appraisals over the past month, relating to the self, the world, and self-blame, rated from 1 (totally disagree) to 7 (totally agree). The PTCI has both strong internal consistency (Cronbach's $\alpha = 0.97$) and high 3-week test–retest reliability (Spearman's ρ correlation = .85).

Due to missing data, at the second assessment, BSI and PDS data were available for nine individuals in the therapy group and seven individuals in the control group, and IPSI and PTCI data were available for nine individuals in the therapy group and six individuals in the control group.

2.3 | Psychotherapy

Trauma-specific psychotherapy was performed by psychotherapists and psychotherapy-specialized senior psychiatrists in single sessions using Eye Movement Desensitization and Reprocessing Therapy (EMDR). EMDR is one of the most common therapeutic interventions for PTSD (Foa, Keane, & Friedman, 2000) and is known to effectively reduce symptoms in the majority of individuals directly following completion of therapy (Seidler & Wagner, 2006; Shapiro, 1989, 1996). Participants completed two individual trauma-specific EMDR sessions of 120 min each per week. During each EMDR session, the participant is asked to imagine the traumatic event, along with all accompanying emotional sensations while simultaneously engaging in periodic eye movements by attending to a moving visual stimulus controlled by the therapist. Furthermore, maladaptive, destructive cognition is identified, edited and corrected, and replaced by constructive cognition. The therapeutic goal is to integrate the traumatic event as a past event into the patient's life history, and in many cases, post-traumatic growth, or positive change experienced as a result of a struggle with adversity, is also achieved. In addition to trauma-focused individual therapy detailed above, participants also completed psychoeducation group sessions (250 min per week), occupational therapy (100 min per day), relaxation therapy (progressive muscle relaxation, Jacobson, 1938, 50 min per day), sports therapy (50 min per day), and physiotherapy (100 min per week).

2.4 | Scanning procedure

Structural images were collected with a 3 Tesla Siemens Magnetom TrioTim scanner (Erlangen, Germany) using a standard 12-channel head coil. The images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI protocol (www.adni-info.org; repetition time = 2,500 ms; echo time = 4.77 ms; TI = 1,100 ms, acquisition matrix = 256 × 256 × 176, flip angle = 7; 1 × 1 × 1 mm^3 voxel size).

2.5 | MRI Data analysis

Structural data were processed with voxel-based morphometry (VBM8, http://dbm.neuro.uni-jena.de/vbm.html) and statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) using default parameters running on MATLAB 9.1 (MathWorks, Sherborn, MA, USA). VBM is a neuroimaging analytic technique that allows investigation of focal differences in brain anatomy based on statistical parameter mapping of structural images. It involves bias correction, tissue classification, and affine registration. Images were normalized to the Montreal Neurological Institute (MNI) space using the ICBM152 template (Mazziotta et al., 2001) and segmented into gray matter, white matter, and cerebrospinal fluid based on voxel signal

intensity and a priori expectation of tissue type based on anatomical location, using default parameters. Modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. Images were smoothed with a full width at half maximum (FWHM) kernel of 8 mm.

Region-of-interest analysis was conducted. To test the association between PTSD symptoms and brain regions implicated in PTSD, we extracted gray matter volume from the hippocampus and amygdala. Separate anatomical masks for the bilateral hippocampus and amygdala were defined using the anatomical automatic labeling (AAL; Tzourio-Mazoyer et al., 2002) template (Figure 1a). The region of interest extraction (REX) toolbox (Whitfield-Gabrieli, 2009) was used to extract gray matter volumes from the identified clusters.

3 | RESULTS

Independent sample *t* tests were conducted to assess baseline differences in demographic variables between the therapy and control groups. The groups showed no significant differences in age, combat experiences, duration of military deployment, or in the time interval between pretherapy and post-therapy assessments (Table 1).

Five participants did not undergo the second MRI assessment. Independent sample *t* tests were also conducted to assess baseline differences in demographic variables and psychological symptoms between dropouts and completers. The groups showed no significant differences in age, combat experiences, duration of military deployment, or scores on any of the psychological questionnaires.

Repeated measures ANOVA were conducted to assess change in psychological symptoms and gray matter volume

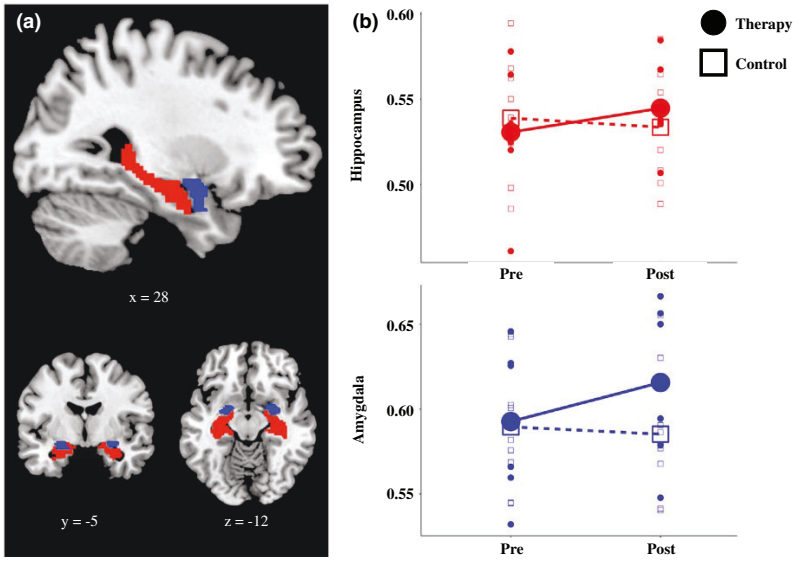

FIGURE 1 Bilateral hippocampal and amygdala gray matter volume. (a) Separate anatomical masks for the bilateral hippocampus (red) and amygdala (blue) were defined using the anatomical automatic labeling (AAL; Tzourio-Mazoyer et al., 2002) template. Montreal Neurological Institute coordinates are provided below each brain image. (b) Gray matter values were extracted for the bilateral anatomical hippocampus and amygdala, and differences between the therapy and control group were assessed using a repeated measures ANOVA. The group by time interaction was significant for the hippocampus ($F(1,13) = 7.33$, $p < .05$, $\eta_p^2 = 0.36$) and close to significance for the amygdala ($F(1,13) = 2.92$, $p = .11$, $\eta_p^2 = 0.18$)

TABLE 1 Demographic information collected at the pretherapy assessment

Variable	Therapy group ($n = 11$)	Control group ($n = 9$)	*t* test
Age (years)	27.4 ± 2.5	29.6 ± 8.8	$t(18) = -0.79$, $p = .488$
Military deployment (days)	211 ± 78.2	216 ± 117	$t(18) = -0.10$, $p = .918$
MHAT-CES[a]	67.8 ± 31.5	54.3 ± 31.0	$t(14) = 0.83$, $p = .419$
Assessment interval (days)[b]	39.4 ± 19.9	49.7 ± 21.9	$t(16) = -1.04$, $p = .316$

Means and standard deviations are displayed for demographic information collected at the first assessment, along with independent samples *t* tests (two-tailed).

[a]MHAT-CES data were available for ten individuals in the therapy group and six individuals in the control group.

[b]Assessment interval data were available for nine individuals in the therapy group and nine individuals in the control group who completed either the second MRI or questionnaire assessment, or both. MHAT-CES, Mental Health Advisory Team Combat Experiences Score.

between groups from pretherapy assessment to post-therapy assessment. There was no main effect of time on gray matter in either the hippocampus or amygdala. However, there was a significant group by time interaction for the hippocampus ($F(1,13) = 7.33$, $p < .05$, $\eta_p^2 = 0.36$) and a nonsignificant trend for the amygdala ($F(1,13) = 2.92$, $p = .111$, $\eta_p^2 = 0.18$; Table 2 and Figure 1b). We also conducted paired *t* tests for each group separately. The increase in hippocampal volume from assessment 1 to assessment 2 in the therapy group was significant ($t(5) = -2.11$, $p = .045$, one-tailed), while the decrease in the control group was not ($t(8) = 1.39$, $p = .102$, one-tailed), while the increase in amygdala volume from assessment 1 to assessment to was not significant for either the therapy ($t(5) = -1.316$, $p = .123$, one-tailed) or in the control group ($t(8) = 0.690$, $p = .255$, one-tailed).

Scores on all psychological questionnaire scores showed a decrease (either significant at $p < .05$ or a trend toward significance) between the pretherapy and post-therapy assessments in both groups, but no group by time interaction was observed for any of the symptom scores (Table 2 and Figure 2). We also conducted paired samples *t* tests for each group separately. The therapy groups showed a significant reduction across all questionnaires (BSI; $t(8) = 2.362$, $p = .023$, one tailed, PDS; $t(8) = 2.205$, $p = .029$, one tailed, IPSI; $t(8) = 1.940$, $p = .044$, PTCI; $t(8) = 2.767$, $p = .012$), while the control group only showed a significant reduction on the PDS questionnaire (BSI; $t(6) = 0.587$, $p = .289$, one tailed, PDS; $t(6) = 2.284$, $p = .031$, one tailed, IPSI; $t(5) = 0.648$, $p = .273$, PTCI; $t(5) = 1.402$, $p = .110$).

Analysis revealed no significant correlations between hippocampal or amygdala gray matter volume and psychological symptoms, either across all participants or separately for each group.

4 | DISCUSSION

Patients with combat-related PTSD were assessed with psychological questionnaires and structural MRI neuroimaging at two time points approximately 6 weeks apart. Individuals who underwent psychotherapy between the two assessments were compared with a waiting-list control group. Psychological symptoms significantly decreased for both groups over time, but no group by time interaction was observed. At the neural level, gray matter volume was assessed in the hippocampus and amygdala, two regions previously implicated in PTSD. No significant effect of time on gray matter volume was found; however, a group by time interaction was observed; the therapy group showed an increase in hippocampal gray matter volume, while the control group did not.

The hippocampus is one of the only sites of neurogenesis in the adult human brain (Eriksson et al., 1998) and has been shown to be highly plastic to environmental effects (Cotman & Berchtold, 2002; Draganski et al., 2006; Kempermann, Kuhn, & Gage, 1997). Neurogenesis in the hippocampus has been shown to modulate forgetting (Akers et al., 2014), while therapeutic interventions for depression and anxiety disorders increase hippocampal neurogenesis (Malberg, Eisch, Nestler, & Duman, 2000; Perera et al., 2007), and hippocampal neurogenesis is required for the behavioral effects of antidepressants (Santarelli, 2003). As such, the hippocampus and hippocampal neuroplasticity may also play a key role in resilience and recovery from stress. This is supported by the current finding that hippocampal volume increased following psychological therapy.

The current findings suggest that in the short term, some PTSD symptoms may reduce, even without therapeutic intervention. Psychological symptoms reduced across all questionnaires for the therapy group, while scores on the PDS also reduced in the control

TABLE 2 Psychological questionnaires and region of interest gray matter

					RM ANOVA	
	Group (*n*)	Pre	Post	*t* test	Time	Time × group
BSI-GSI	Therapy (9)	85.6 ± 26.4	70.2 ± 30.3	$t(8) = 2.362$, $p = .023$	$F(1,14) = 4.69$, $p < .05$, $\eta_p^2 = 0.25$	$F(1,14) = 2.67$, $p = .13$, $\eta_p^2 = 0.16$
	Control (7)	71.6 ± 38.3	69.4 ± 41.8	$t(6) = 0.587$, $p = .289$		
PDS	Therapy (9)	34.4 ± 7.28	28.1 ± 12.0	$t(8) = 2.205$, $p = .029$	$F(1,14) = 10.01$, $p < .01$, $\eta_p^2 = 0.42$	$F(1,14) = 0.049$, $p = .82$, $\eta_p^2 = 0.003$
	Control (7)	31.2 ± 14.1	24.0 ± 14.5	$t(6) = 2.284$, $p = .031$		
PTCI	Therapy (9)	132.8 ± 30.2	108.8 ± 33.1	$t(8) = 2.767$, $p = .012$	$F(1,13) = 7.85$, $p < .05$, $\eta_p^2 = 0.38$	$F(1,13) = 0.05$, $p = .82$, $\eta_p^2 = 0.004$
	Control (6)	125.5 ± 22.6	105.2 ± 46.9	$t(5) = 1.402$, $p = .110$		
IPSI	Therapy (9)	3.8 ± 1.3	3.2 ± 1.1	$t(8) = 1.940$, $p = .044$	$F(1,13) = 2.97$, $p = .11$, $\eta_p^2 = 0.19$	$F(1,13) = 0.49$, $p = .50$, $\eta_p^2 = 0.036$
	Control (6)	3.2 ± 1.0	3.0 ± 1.5	$t(5) = 0.648$, $p = .273$		
Hippocampus	Therapy (6)	0.53 ± 0.04	0.55 ± 0.03	$t(5) = -2.11$, $p = .045$	$F(1,13) = 1.49$, $p = .24$, $\eta_p^2 = 0.10$	$F(1,13) = 7.33$, $p < .05$, $\eta_p^2 = 0.36$
	Control (9)	0.54 ± 0.03	0.53 ± 0.03	$t(8) = 1.39$, $p = .102$		
Amygdala	Therapy (6)	0.59 ± 0.05	0.61 ± 0.05	$t(5) = -1.316$, $p = .123$	$F(1,13) = 1.37$, $p = .26$, $\eta_p^2 = 0.095$	$F(1,13) = 2.92$, $p = .11$, $\eta_p^2 = 0.18$
	Control (9)	0.59 ± 0.04	0.58 ± 0.04	$t(8) = 0.690$, $p = .255$		

Means and standard deviations are displayed for psychological questionnaire data and region-of-interest gray matter, collected at the first (Pre) and second (Post) assessment, separately for the therapy and waiting-list control groups, along with paired samples *t* tests (one-tailed) and repeated measures ANOVA. RM ANOVA, repeated measures analysis of variance; BSI-GSI, Brief Symptom Inventory Global Severity Index; PDS, Posttraumatic Diagnostic Scale; PTCI, Posttraumatic Cognitions Inventory; IPSI, Interpretation of PTSD Symptoms Inventory; η_p^2, partial eta-squared.

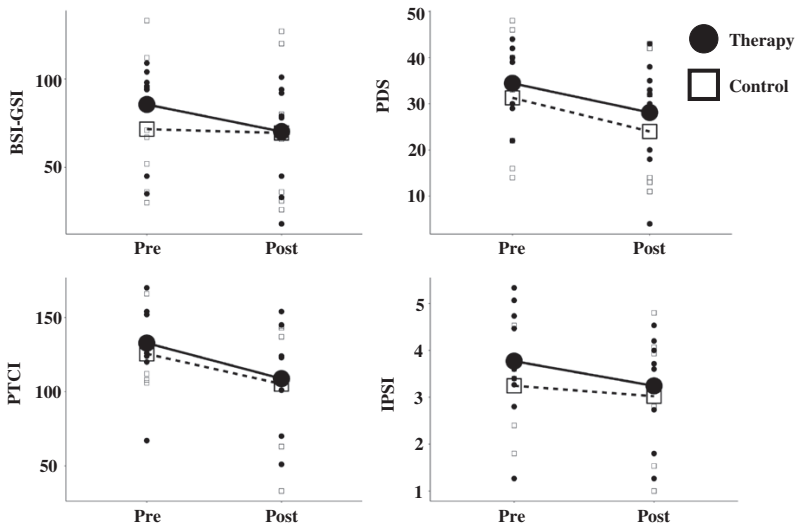

FIGURE 2 Psychological questionnaire scores. Psychological distress and PTSD symptoms were measured at both time points. Differences between the therapy and control group were assessed using a repeated measures ANOVA. There was a significant main effect of time for the BSI-GSI ($F(1,14) = 4.69$, $p < .05$, $\eta_p^2 = 0.25$), PDS ($F(1,14) = 10.0$, $p < .01$, $\eta_p^2 = 0.42$), PTCI ($F(1,13) = 7.85$, $p < .05$, $\eta_p^2 = 0.38$) and a trend toward significant for the IPSI ($F(1,13) = 2.97$, $p = .11$, $\eta_p^2 = 0.19$). There was no significant group by time interaction for any of the questionnaire scores. BSI-GSI, Brief Symptom Inventory Global Severity Index; PDS, Posttraumatic Diagnostic Scale; PTCI, Posttraumatic Cognitions Inventory; IPSI, Interpretation of PTSD Symptoms Inventory

group. Although the mechanisms underlying the reduction in symptoms in the waiting-list control group remain unclear, one possibility is that some individuals experienced spontaneous remission. Reductions of PTSD symptoms have previously been observed in individuals who have not received treatment (Güveli et al., 2006; Kessler, 1995). In addition, reductions in PTSD symptoms may be longer lasting when accompanied with increases in hippocampal volume. Further longitudinal work with multiple assessment points after completion of therapy would be useful to assess how increases in hippocampal gray matter volume may relate to long-lasting reductions of psychological symptoms.

In a study with a similar design by Lindauer et al. (2005), patients in a therapy group showed a significant reduction in symptoms, but no change in hippocampal or amygdala volume compared with a waiting-list control group. Although the approach and the sample size ($N = 18$) of the study by Lindauer and colleagues are comparable to the current study, one potential reason for the discrepancy between the results may be due to the use of different populations. In the current study, all participants were male, had experienced combat-related trauma, and the mean age was 28 ($SD = 6$), while in the study by Lindauer and colleagues, over 50% of the participants were female, participants reported exposure to interpersonal violence or accidents or disasters, and the average age was 40 ($SD = 9$). Age and gender are known to play a key role in hippocampal neuroplasticity (Kuhn, Dickinson-Anson, & Gage, 1996; Lisofsky et al., 2015) and resilience to stress (McEwen, 2002; McEwen & Morrison, 2013), while military and civilian populations have been shown to differ in risk factors (Brewin, Andrews, & Valentine, 2000) and response to psychotherapy (Bradley, Greene, Russ, Dutra, & Westen, 2005). If the effects of psychological therapy on the hippocampus are mediated by factors such as age, gender, or type of trauma, then the use of more homogeneous samples may be preferable to delineate these effects.

One should also note that the magnetic field strength employed by the two studies differs. Lindauer et al. (2005) analyzed images from a 1.5 Tesla scanner, while in the current study, images were collected using a 3 Tesla scanner. As such, the higher signal-to-noise ratio of the images in the current study, as well as other advancements in MRI image acquisition over the last decade, may have provided us with greater sensitivity to detect small effect sizes.

Participants were assessed twice, prior to therapy and directly following therapy, with an interval of approximately 6 weeks between assessments. Recent work on human brain plasticity with multiple neuroimaging assessments has demonstrated that brain regions undergo a period of expansion followed by renormalization during training interventions (Wenger, Brozzoli, Lindenberger, & Lövdén, 2017; Wenger et al., 2016), and that after a period of 6 weeks, gray matter volume has already begun to renormalize following initial expansion (Wenger et al., 2016). Although this work has focused on skill acquisition, it is also possible that therapeutic interventions may have stronger or wider effects on the brain at earlier stages in the treatment. Future studies may seek to incorporate multiple assessments during the therapy period to allow closer tracking of therapy-related gains, and this may reveal greater effects than those currently observed.

The study has a number of potential limitations. Not all participants were available for follow-up assessment. Although completers and dropouts did not differ significantly in their demographic or psychological characteristics at the initial assessment, there may be some nonrandom selection effects that are not captured by these variables. One should note that the size of the participant group may also limit the generalizability of the current findings. Given the relatively small sample size and explorative nature of this pilot study, we have interpreted both results significant at $p < .05$, and results that show a trend toward significance, as these findings may prove informative for future studies. In addition, due to the current sample size, we only conducted a region-of-interest analysis, which necessarily restricts analysis toward a priori hypothesized regions. Future work may seek to replicate the current findings with larger samples and extend them using a whole-brain approach.

To our knowledge, this is the first study to compare combat-related PTSD patients before and after therapy to a waiting-list control group. In contrast to previous work, we find evidence for increases in gray matter volume in the hippocampus in response to psychological therapy. In the current study, we assessed combat-exposed young adult males, while previous work assessed both male and female civilians with a larger age range. It is possible that age, gender, and military status may mediate the effect of psychological therapy on gray matter volume. Future work may seek to define and compare neural changes following therapy in female, older adult, and civilian populations.

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CONFLICT OF INTEREST

None declared.

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Paper V

Butler, O., Herr, K., Willmund, G., Gallinat, J., Kühn, S., Zimmermann, P. (under review). Trauma, Treatment and Tetris: Video gaming increases hippocampal volume in combat-related posttraumatic stress disorder.

Trauma, Treatment and Tetris: video gaming increases hippocampal volume in combat-related post-traumatic stress disorder

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ABSTRACT

Background. Recent work has demonstrated the utility of Tetris as a preventative intervention to reduce intrusive memories of a traumatic event. However, no study to date has assessed Tetris in a clinical setting, with patients with existing posttraumatic stress disorder (PTSD).

Methods. Patients with combat-related PTSD were recruited prior to onset of psychotherapy and were randomly assigned either to an experimental Tetris and therapy group or a therapy-only control group. In the control group, participants completed treatment as usual - Eye Movement Desensitization and Reprocessing (EMDR) psychotherapy. In the Tetris group, in addition to EMDR, participants also played 60 minutes of Tetris every day. Participants completed structural MRI and psychological questionnaires prior to and following completion of therapy, approximately six weeks later. In addition, psychological questionnaire data was collected at follow-up, approximately six months later.

Results. Increases in hippocampal volume following therapy were observed in the Tetris group but not the control group. In addition, hippocampal increases correlated with reduction of PTSD, depression and anxiety symptoms between completion of therapy and follow-up assessment, in the Tetris group but not the control group.

Conclusions. We find evidence that Tetris may be useful as a therapeutic intervention for PTSD, alongside EMDR psychotherapy. Tetris-related increases in hippocampal volume may ensure that therapeutic gains are maintained following completion of therapy.

INTRODUCTION

Recent work has provided first evidence of the utility of the visuospatial video game Tetris as an early therapeutic intervention for posttraumatic stress disorder (PTSD) (Holmes, James, Coode-Bate, & Deeprose, 2009; Holmes, James, Kilford, & Deeprose, 2010; Horsch et al., 2017; Iyadurai et al., 2017). Holmes and colleagues have shown that playing Tetris directly following trauma exposure can reduce subsequent intrusive memories of the traumatic event, and have demonstrated the efficacy of this "cognitive vaccine" in both experimental (Holmes et al., 2009, 2010) and real-world settings (Horsch et al., 2017; Iyadurai et al., 2017).

Following exposure to an event, the memory trace of that event must be consolidated into long-term memory in order for it to be accessible for later recall (McGaugh, 2000). In the first few hours following the event, the memory trace remains in a labile state, as it is consolidated, and is susceptible or vulnerable to interference (Wixted, 2004). Performing an unrelated task while memory for an event is in a labile state can reduce subsequent retrieval (Walker, Brakefield, Hobson, & Stickgold, 2003). Holmes and colleagues propose that by completing a demanding visuospatial task during the period of memory consolidation for a traumatic event, the memory trace is weakened due to competition for the cognitive resources required for consolidation (Holmes et al., 2009).

To date, work using Tetris as an intervention has focused on attempting to disrupt consolidation of the traumatic memory, either within the first six hours (Holmes et al., 2009, 2010; Horsch et al., 2017; Iyadurai et al., 2017) following the trauma exposure, or the next day (James et al., 2015). However, playing a video game in the direct aftermath

of a traumatic event is neither practical nor possible in every case. In addition, no study to date has assessed individuals with existing PTSD. It is estimated that there are currently around 8 million adults with PTSD in the US alone (Kessler et al., 2005; Kilpatrick et al., 2013). As such, interventions for individuals who are already experiencing post-traumatic symptoms are sorely required. In the current study, we investigate the utility of Tetris as an adjunct therapeutic intervention for individuals with current PTSD.

Current therapeutic interventions for PTSD have a number of limitations regarding response rates and long-term efficacy. A significant minority of individuals will not show a significant improvement in symptoms directly following therapy, with rates of non-responders estimated to be as high as 35 to 50% in some studies (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Bradley, Greene, Russ, Dutra, & Westen, 2005; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). In addition, long-term prognosis for PTSD is poor, with a majority of individuals continuing to experience symptoms for months or years after initial diagnosis, and a substantial number of individuals never fully recovering (Kessler, 1995). As such, there is a significant need for additional therapeutic interventions that may act as an adjunct to traditional psychotherapy for non-responders and to ensure the long-term maintenance of therapy-related gains for responders.

At the neuroanatomical level, adult PTSD populations are characterized by smaller volumes in the hippocampus and in prefrontal regions including the ventromedial prefrontal cortex (vmPFC) and the anterior cingulate cortex (ACC) (Karl et al., 2006; Kitayama, Vaccarino, Kutner, Weiss, & Bremner, 2005; Kühn & Gallinat, 2013). The hippocampus is involved in memory, learning and fear extinction (Pohlack et al., 2012;

Squire, 1992), while the vmPFC and ACC are involved in affective and cognitive processing and the regulation of fear expression (Etkin, Egner, & Kalisch, 2011). Smaller hippocampal volumes have been associated with increased risk for PTSD (Gilbertson et al., 2002) and with poorer prognosis (Apfel et al., 2011; Chao, Yaffe, Samuelson, & Neylan, 2014; Rubin et al., 2016; van Rooij et al., 2015), while smaller volumes in the prefrontal cortex may represent a more general effect of stress exposure (Butler et al., 2017, 2018; Kasai et al., 2008).

At a structural level, the hippocampus is one of the most plastic regions in the human brain (Cotman & Berchtold, 2002; Draganski et al., 2006; Kempermann, Kuhn, & Gage, 1997), as well as being one of the only sites of adult neurogenesis (Eriksson et al., 1998). The hippocampus is rich in glucocorticoid receptors making it highly susceptible to the effects of stress. Stress has been shown to produce dendritic atrophy and reductions in neurogenesis in the hippocampus (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen & Morrison, 2013; Sapolsky, Krey, & McEwen, 1985; Sapolsky, Uno, Rebert, & Finch, 1990), and stress induced alterations in the hippocampus have been linked to reductions in memory and cognition (Kim, Diamond, Haven, & Blvd, 2002; McEwen & Sapolsky, 1995) and increases in anxiety related behavior (Lagace et al., 2010). Conversely, training studies have demonstrated that increases in hippocampal volume can be produced with a wide variety of interventions (Draganski et al., 2006; Erickson et al., 2011) including video gaming interventions (Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014). The hippocampus is also involved in spatial orientation and navigation, and spatial learning has been linked to increases in hippocampal volume (Kühn & Gallinat, 2014; Maguire et al., 2000; Woollett & Maguire, 2011). As such, sustained

playing of a demanding visuospatial task such as Tetris can be expected to produce increases in hippocampal volume, driven in part by increases in neurogenesis. In animal models, hippocampal neurogenesis has been shown to mediate forgetting and support new learning (Akers et al., 2014). Newly formed neurons compete with existing neurons for connections, and these newly formed connections may come to replace old ones, weakening existing memories and strengthening new ones (Akers et al., 2014; Yasuda et al., 2011). Therefore, we propose that video gaming related increases in hippocampal neurogenesis may lead to subsequent reductions in PTSD symptoms by weakening memories of the traumatic event and strengthening memories formed during therapy.

In the current study, we investigated the structural and behavioral effects of a Tetris intervention in individuals with PTSD undergoing psychotherapy, using a prospective design. Individuals with combat-related PTSD were recruited and assessed prior to and directly following Eye Movement Desensitization and Reprocessing (EMDR) therapy (Shapiro, 1989, 1996), and at follow-up, approximately six months later. Individuals in the control group completed therapy as normal, while individuals in the experimental group completed a Tetris intervention in addition to therapy, playing 60 minutes of Tetris per day. During each EMDR session, the individual was asked to re-experience the traumatic event, while attending to a moving stimulus. We propose that playing Tetris following therapy, while the re-activated traumatic memory is in a labile state, should weaken reconsolidation and aid recovery (James et al., 2015). One should note that playing Tetris has been shown to reduce the vivid, intrusive elements of a traumatic memory, but not declarative memory (Holmes et al., 2009). As such, Tetris should not affect memory of the therapy sessions, nor interfere with the clinical efficacy

of EMDR. In addition, spatial memory training and video gaming have been linked to increases hippocampal volume (Kühn et al., 2014; Woollett & Maguire, 2011) and increases in hippocampal volume have been associated with improvements in memory and reductions in symptoms in PTSD (Bremner & Vermetten, 2004; Levy-Gigi, Szabó, Kelemen, & Kéri, 2013). As such, Tetris may aid in the recovery of PTSD both by weakening the memory of the traumatic event, and by increasing hippocampal volume. We hypothesize that the Tetris group will show increases in hippocampal volume and reductions in symptoms both directly following completion of therapy and at follow-up.

MATERIALS AND METHODS

Participants

Forty participants with combat-related PTSD were recruited from the German Federal Armed Forces prior to onset of therapy. All participants were inpatients at the German Military Hospital, Berlin, Germany. All participants were male and had been deployed overseas to areas of conflict. As inclusion criteria, participants were screened by both clinical psychologists and psychiatrists for the presence of mission-related trauma within the last two years and for a current diagnosis of PTSD according to ICD-10 criteria. As exclusion criteria, participants were also screened for current or previous comorbid psychosis or substance abuse, use of psychotropic medication, a history of concussion or traumatic brain injury, and MRI contraindications. Patients were assessed for inclusion and exclusion criteria and then randomly assigned to either the experimental Tetris group (n=20) or the control group (n=20). A sample size of 20 per group provides 80% power to detect a between-group difference with an effect size of d = 0.91, as found by Holmes and colleagues (2009) at a 5% significance level (two-tailed). The local ethics committee of Charité University Clinic, Berlin, Germany, approved of the study and written informed consent was obtained from each participant prior to participation, in line with the declaration of Helsinki.

Participants in both groups completed EMDR therapy (Shapiro, 1989, 1996). Participants in the control group completed EMDR therapy only, while participants in the experimental Tetris group also played the video game Tetris for sixty minutes per day. Following completion of therapy, approximately six weeks later, all participants returned for neuroimaging and questionnaire assessment. In addition, participants completed the

questionnaire assessment only, approximately six-months following completion of therapy. Four participants, 2 in the Tetris group and 2 in the control group, did not complete the six-month follow-up assessment.

EMDR

All participants completed EMDR therapy. EMDR is one of the most common therapeutic interventions for PTSD (Foa, Keane, & Friedman, 2000), and is known to effectively reduce symptoms in the majority of individuals directly following completion of therapy (Seidler & Wagner, 2006; Shapiro, 1989, 1996). Participants completed an average of 7.2 sessions (SD = 1.8) of 60 to 90 minutes each, over the course of approximately six weeks (average duration 39.9 days, SD = 4.8). In instances where number of sessions was not available from the clinical records (n = 3), participant self-report data was used. Each EMDR session consists of selecting a memory to work on. The selected memory is then reactivated, during which time the individual attends briefly to certain elements of the memory, while simultaneously engaging in a periodic set of eye movements by attending to a moving visual stimulus controlled by the therapist.

Tetris Intervention

Participants in the Tetris group were provided with a Nintendo DS XL console and the computer game Tetris. Participants were requested to play for 60 minutes per day. Participants reported playing an average of 61 minutes (SD = 14.6, data not available for 2 participants) per day, and missing an average of one day (SD = 1.2, data not available for 2 participants). On days that participants completed a therapeutic session, participants were required to play Tetris within a six-hour window following completion of therapy.

Questionnaires

To assess duration of military deployment and experiences during deployment, participants completed a German version of the Combat Experiences Scale (CES), a 33-item questionnaire assessing the type and frequency of combat related events during military deployment (Guyker et al., 2013), as well as a study-specific questionnaire that included items on the number and duration of military deployments.

To assess psychological symptoms, prior to each neuroimaging session participants also completed German versions of the following self-report questionnaires; the Posttraumatic Diagnostic Scale, the Beck's Depression Inventory and the State Trait Anxiety Inventory.

The PDS is designed to aid in the diagnosis of PTSD and assess symptom severity (Ehlers, Steil, Winter, & Foa, 1996; Foa, Cashman, Jaycox, & Perry, 1997). As part of the PDS, respondents rate 17 items representing the main symptoms of PTSD experienced in the past 30 days, on a four-point scale, ranging from 0 ("not at all or only one time") to 3 ("5 or more times a week / almost always").

The BDI-II is a 21-item inventory assessing characteristic behaviors and symptoms of depression experienced in the past two weeks, on a four-point scale, ranging from 0 (e.g. "I do not feel sad") to 3 ("I am so sad or unhappy I can't stand it") (Beck, Steer, & Brown, 1996; Hautzinger, Bailer, H., & Keller, 1994).

The STAI-G comprises of two forms, assessing state anxiety, experienced currently (Form X-1), and trait anxiety, experienced in general (Form X-2) (Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, 1983). In the current study, we use the trait anxiety subscale of the STAI, Form X-2, as we are interested in assessing

changes in enduring rather than temporary states of anxiety and stress. In Form X-2, individuals rate 20 statements describing emotions of stress and worry, on a four-point scale, ranging from 1 (“almost never”) to 4 (“almost always”).

Scanning procedure

Structural images were acquired using a 3 T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) and a 12-channel radiofrequency head coil. The images were obtained using a three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI protocol (www.adni-info.org; TR = 2500 ms; TE = 4.77 ms; TI = 1100 ms, acquisition matrix = 256 × 256 × 176, flip angle = 7°; 1 × 1 × 1 mm^3 voxel size).

MRI Data analysis

Structural data were processed with the computational anatomy toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/) and statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spmb) using default parameters running on MATLAB 9.1 (Mathworks, Sherborn, MA). Voxel based morphometry (VBM) was used to estimate the local amount, or volume of gray matter (Ashburner & Friston, 2005). VBM is a neuroimaging analytic technique that allows investigation of focal differences in brain anatomy based on statistical parameter mapping of structural images. It involves bias correction, tissue classification, and affine registration. Images were normalized to the Montreal Neurological Institute (MNI) space using the ICBM152 template (Mazziotta et al., 2001) and segmented into gray matter, white matter, and cerebrospinal fluid using

default parameters. Modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. Images were smoothed with a full width at half maximum (FWHM) kernel of 8 mm.

A whole-brain voxel-wise factorial analysis was computed (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). Age and total inter-cranial volume were included as covariates of no interest, and an absolute gray matter probability threshold of 0.2 was applied (CAT 12 manual, http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). The resulting maps were thresholded at $p < 0.001$ at the voxel level and cluster-extent thresholded at 100 voxels per cluster to control for type-I error.

We also conducted region of interest (ROI) analysis in the hippocampus, a region commonly implicated in adult PTSD (Apfel et al., 2011; Bremner et al., 1995; Chao et al., 2014; Gilbertson et al., 2002; Lindauer et al., 2005; Rauch, Shin, & Phelps, 2006; Rubin et al., 2016; Shin, Rauch, & Pitman, 2006; van Rooij et al., 2015; Vythilingam et al., 2002). A bilateral anatomical hippocampal mask for the hippocampus was defined using the anatomical automatic labeling (AAL) (Tzourio-Mazoyer et al., 2002) template. A PTSD specific hippocampal mask was defined using the hippocampal cluster identified in a previous meta-analysis of whole-brain neuroimaging studies (Kühn & Gallinat, 2013). The Region-of-Interest Extraction (REX) Toolbox (Whitfield-Gabrieli, 2009) was used to extract gray matter volumes from the identified clusters.

We also assessed the relationship between increases in hippocampal volume and subsequent reductions in symptoms. We calculated change in the hippocampus by subtracting pre-therapy hippocampal gray matter volume from post-therapy hippocampal

gray matter volume, from the cluster identified in the whole brain analysis, where positive values indicate increases in hippocampal volume following completion of therapy. We also calculated change in symptoms by subtracting scores at follow-up for the PDS, BDI and STAI from post-therapy scores, where negative values indicate decreases in symptoms from completion of therapy to follow-up. We then correlated these change scores separately for each group.

RESULTS

Participants

The Tetris and control groups did not differ in age, gender, duration of military deployments, combat exposure, number of EMDR sessions or interval between assessments (see Table 1).

Table 1. Demographic information

Variable	Tetris	Therapy Only	t-test
Age (years)	34.2 (7.3)	32.5 (5.3)	t(38)=0.791, *p*=0.434
Military Deployment (days)	354.9 (305.6)	345.9 (214.2)	t(38)=0.108, *p*=0.915
CES	32.2 (12.9)	34.4 (16.7)	t(38)=0.601, *p*=0.550
EMDR Sessions	7.0 (1.6)	7.3 (1.9)	t(38)=0. 621 *p*=0.538
Pre/ Post Interval (days)	39.9 (4.8)	36.8 (6.6)	t(38)=1.736, *p*=0.091
*Post/ Follow-Up Interval (days)	204.1 (57.4)	256.4 (138.5)	t(34)=1.481, *p*=0.148

*Follow-up data was missing for 4 participants (2 Tetris, 2 therapy-only controls).
CES; Combat Experiences Scale

Neuroimaging analyses

Whole brain analysis revealed a significant increase in gray matter volume in a cluster in the right hippocampus (k = 150, x = 27, y = -33, z = -3, $p < 0.001$ at the voxel level, and k > 100, non-isotropic smoothness corrected at the cluster level, see Figure 1) in the Tetris group following therapy, compared to the control group.

ROI analysis also revealed a significant group by time interaction, with larger volumes in the Tetris group following therapy than the control group, in the hippocampal cluster identified in a meta-analysis of PTSD neuroimaging studies where PTSD patients were compared with trauma-exposed controls (Kühn & Gallinat, 2013, $F(1,38)=4.419$, $p = 0.042$), and the bilateral anatomical hippocampus defined using the anatomical automatic labelling (AAL) template (Tzourio-Mazoyer et al., 2002) ($F(1,38)=7.07$, $p = 0.011$, Supplementary Figure 1).

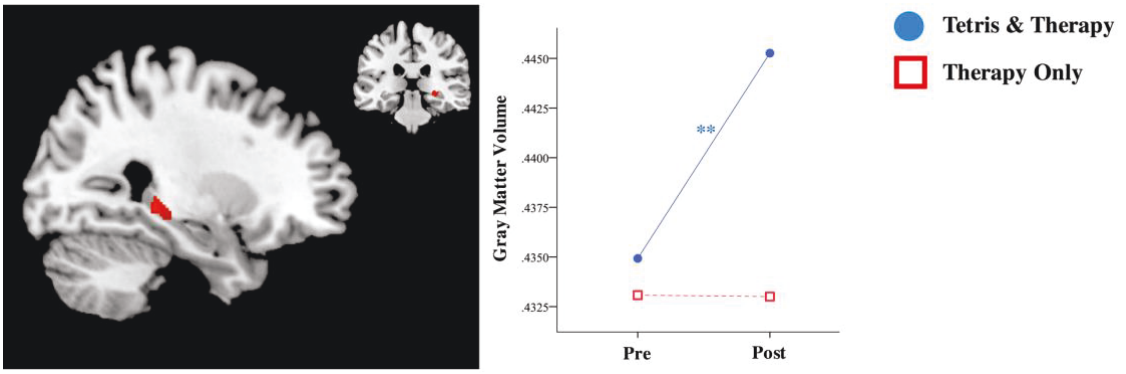

Figure 1.

Neuroimaging results of whole brain analysis. Brain image displays the cluster from a whole-brain analysis across all participants, comparing increases in the Tetris group following therapy, to the therapy-only control group (k = 150, x = 27, y = -33, z = -3, $p <$ 0.001 at the voxel level, and k > 100, non-isotropic smoothness corrected at the cluster level).

Psychological questionnaire analyses

Repeated measures ANOVA revealed a main effect of time, with significant reductions in PTSD symptoms (PDS, $F(2,68)= 7.198$, $p = 0.001$) and trait anxiety (STAI-G Form X-2, $F(2,68)= 3.641$, $p = 0.031$), and a statistical trend for reductions in depression symptoms (BDI, $F(2,68)= 2.674$, $p = 0.076$). The group by time interaction was not significant for the PDS ($F(2,68)= 0.272$, $p = 0.763$) or BDI ($F(2,68)= 0.268$, $p = 0.765$), but there was a significant interaction for the STAI ($F(2,68)= 3.153$, $p = 0.049$). We then conducted post-hoc paired sample t-tests to compare pre-therapy symptom levels to those at six-month follow-up. Both groups continued to show a significant improvement in PTSD symptoms from pre-therapy levels at six-month follow-up (PDS: Tetris; $t(17) = 1.929$, $p = 0.036$, Control; $t(17) = 3.395$, $p = 0.002$, significance one-tailed). However, only the Tetris group continued to show a significant reduction in anxiety symptoms (STAI: Tetris; (17) $= 1.934$, $p = 0.035$, Control; $t(17) = 0.574$, $p = 0.287$, significance one-tailed) and a trend towards reduction in depression symptoms (BDI: Tetris; $t(17 = 1.003$, $p = 0.165$, Control; $t(17) = 0.239$, $p = 0.407$ significance one-tailed) at six-month follow-up (see Figure 2A).

To explore associations between neural and clinical change we correlated changes in hippocampal volume with changes in psychological symptoms. Using the cluster identified in the whole brain analysis, hippocampal volume increases following therapy correlated with further reduction of symptoms between completion of therapy and follow-up in the Tetris group, but not the control group (see Figure 2B).

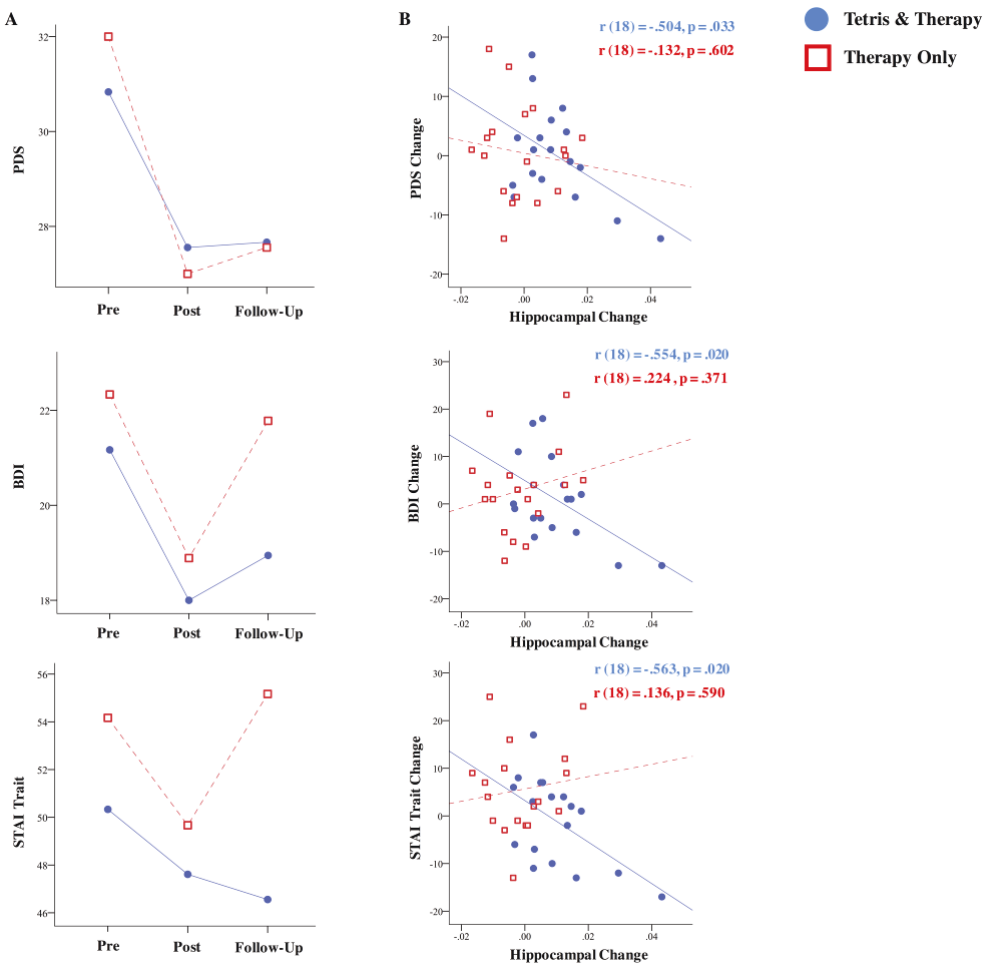

Figure 2.

Psychological questionnaire scores and hippocampal gray matter. (A) Psychological Questionnaire Scores are displayed separately for the Tetris and therapy-only control groups, at three time points; prior to therapy (Pre), directly following therapy (Post) and approximately six months later (Follow-Up). (B) Increases in hippocampal volume following therapy correlated with decreases in symptoms at follow-up, in the Tetris group but not the therapy-only control group. Follow-up data was missing for 4 participants (2 Tetris, 2 therapy-only controls). Analyses based on 36 participants. PDS, Posttraumatic Diagnostic Scale, BDI, Beck's Depression Inventory, STAI; State Trait Anxiety Inventory.

DISCUSSION

We find evidence that completing a visuospatial video-gaming intervention during psychological therapy for PTSD leads to increases in hippocampal volume and maintenance of a wider range of therapy-related gains, with increases in hippocampal volume correlating with further reductions in symptoms at a six-month follow-up. PTSD patients completed structural MRI and psychological questionnaires prior to and following EMDR therapy and psychological questionnaires only at a six-month follow-up. Patients in a control group completed therapy as normal, while patients in an experimental group also completed a visuospatial intervention, playing the video game Tetris every day for the duration of therapy. At the brain structural level, we found larger hippocampal volumes in the Tetris group, at both the whole brain and ROI levels. At the psychological level, directly following therapy both groups showed reductions in PTSD, depression and anxiety symptoms. At the six-month follow-up both groups continued to show lower PTSD symptoms, however only the Tetris group continued to show reduced anxiety and a trend towards reduced depressions symptoms. In addition, hippocampal gray matter increases during therapy correlated with further reductions in PTSD, depression and anxiety symptoms from discharge to follow-up in the Tetris group but not the control group.

Tetris provides a promising therapeutic intervention for a number of practical reasons. The video gaming consoles required are inexpensive, mobile and can be re-used multiple times. Administration does not require a clinician and can even be self-administered. Tetris does not produce adverse side effects, and is enjoyable to play, so compliance is likely to be high. Tetris is also adaptive; as an individual continues to play

the difficulty level (the speed at which the blocks fall) automatically increases until the game ends (the blocks fill the screen), at which point the game restarts at the lowest difficulty. As such, through adaptation of the level of difficulty to the skill of the player, frustration that the game is too difficult and boredom that the game is too easy should be kept at a minimum and the player should remain engaged in the game.

The current study builds on previous work that has employed Tetris as the visuospatial task of choice (Holmes et al., 2009, 2010; Iyadurai et al., 2017; James, Lau-Zhu, Tickle, Horsch, & Holmes, 2016). However other demanding visuospatial working memory tasks, including other video games, may also successfully be used for PTSD. Attention and engagement with a task is known to be a key factor in producing training related gains, at both the behavioral and neural levels (Park & Bischof, 2013; Stefan, Wycislo, & Classen, 2004) Providing a range of games from which an individual could choose could help maintain motivation and compliance, particularly for individuals outside of a clinical setting.

In the current study, we assessed combat-exposed young adult males. It is possible that trauma type, age, gender and military status may mediate the effect of a video gaming intervention on the brain. Gender and age have been shown to play a role in resilience to stress (McEwen, 2002; McEwen & Morrison, 2013) and hippocampal neuroplasticity (Kuhn, Dickinson-Anson, & Gage, 1996; Lisofsky et al., 2015), while military and civilian PTSD populations have been shown to differ in risk factors (Brewin, Andrews, & Valentine, 2000) and response to psychotherapy (Bradley et al., 2005). Future work may seek to explore the utility of video game interventions for female and civilian PTSD populations.

Current interventions for PTSD have a number of limitations regarding response rates and long-term efficacy, and there is a significant need for additional therapeutic interventions that may act as an adjunct to traditional psychotherapy for non-responders and to ensure the long-term maintenance of therapy-related gains for responders. We provide first evidence that Tetris may be useful as intervention for current PTSD, alongside EDMR psychotherapy. Following completion of psychotherapy, symptoms reduced across all participants and both groups continued to show reductions in PTSD symptoms at six-month follow-up. However, only the Tetris group continued to show reductions in anxiety symptoms and a trend towards reductions in depression symptoms at six-month follow-up. Playing Tetris correlated with increases in hippocampal volume, and hippocampal increases correlated with continued reduction of PTSD, depression and anxiety symptoms between completion of therapy and six-month follow-up. As such, Tetris playing may ensure that a wider range of symptom improvements are maintained following therapy, through increases in hippocampal volume.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest with respect to their authorship or the publication of this article. KH, GW and PZ are employed by the German Armed Forces. Their employment had no influence on the study design.

OPEN SCIENCE

Key data and Materials have been made publicly available via the Open Science Framework and can be accessed at osf.io/xz32u, or are otherwise available from the authors on request (with the exception of questionnaire measures subject to third-party copyright or potentially identifying patient information).

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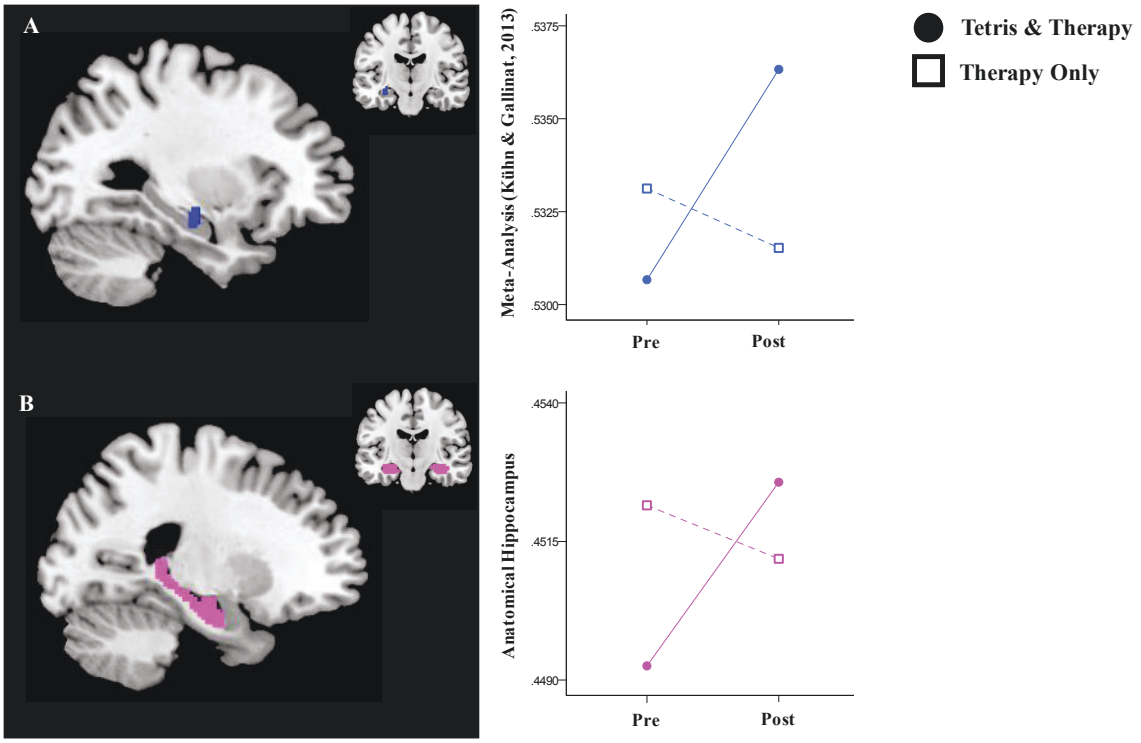
SUPPLEMENTARY RESULTS



Supplementary Figure 1. Region of interest hippocampal volume.

Hippocampal gray matter volume showed a significant group by time interaction, with larger volumes at the post assessment in the Tetris group but not the control group.

A) Left anterior hippocampal cluster identified in a meta-analysis of PTSD neuroimaging studies (Kühn & Gallinat, 2013) **(F(1,38)=4.419, p =0.042)**

B) Bilateral anatomical hippocampus defined using the anatomical automatic labeling (AAL, Tzourio-Mazoyer et al., 2002) template **(F(1,38)=7.07, p =0.011)**

Paper VI

Butler, O., Herr, K., Willmund, G., Gallinat, J., Zimmermann, P., Kühn, S. (under review). Neural correlates of malingering: Larger hippocampal volume correlates with symptom aggravation in combat-related posttraumatic stress disorder.

Neural correlates of malingering: Larger hippocampal volume correlates with symptom aggravation in combat-related posttraumatic stress disorder

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Abstract

The diagnosis of posttraumatic stress disorder (PTSD) is vulnerable to the simulation or exaggeration of symptoms as it depends on the individual's self-report of symptoms. The use of symptom validity tests is recommended to detect malingering in PTSD. However, in neuroimaging research, PTSD diagnosis is often taken at face validity. To date, no neuroimaging study has compared credible PTSD patients with those identified as malingering, and the potential impacts of including malingerers along with credible patients on results is unclear. We classified male patients with combat-related PTSD as either credible (n=37) or malingerers (n=9) based on the Morel Emotional Numbing Test, and compared structural neuroimaging and psychological questionnaire data. Patients identified as malingerers had larger gray matter volumes in the hippocampus, right inferior frontal gyrus and thalamus, and reported higher PTSD symptoms than credible PTSD patients. This is the first structural neuroimaging study to compare credible PTSD patients and malingerers. We find evidence of structural differences between these groups, in regions implicated in PTSD, inhibition and deception. These results emphasize the need for the inclusion of SVTs in neuroimaging studies of PTSD to ensure future findings are not confounded by an unknown mix of valid PTSD patients and malingerers.

Keywords: Symptom validity tests; Symptom exaggeration, Malingering; Military; Structural neuroimaging; MRI

1. Introduction

Posttraumatic stress disorder (PTSD) is a complex and debilitating psychiatric disorder, caused by exposure to traumatic events. PTSD is characterized by hyperarousal, avoidance, and re-experiencing, including intrusive memories and sensory flashbacks of the traumatic event (American Psychiatric Association, 2013). Diagnosis of PTSD is made by a clinical assessment of the nature of the traumatic event, the duration since the event, the symptoms experienced, and the level of functional impairment (American Psychiatric Association, 2013). Since its addition to the DSM III in 1980, the diagnostic use of PTSD has increased to the point where it is now the third most commonly diagnosed disorder by psychologists (Evans et al., 2013).

PTSD occurs in both military and civilian populations. However, prevalence rates and levels of psychopathology appear to be consistently higher in combat-exposed military populations than comparable civilian populations (Herry et al., 2010; Kessler et al., 2014; Thomas et al., 2010; Trautmann et al., 2016; Wittchen et al., 2012). Military conflict is increasing across the globe, leading to a growing number of individuals who are exposed to combat trauma and extreme stress. PTSD is one of the most prevalent psychiatric disorders in veterans (Tanielian et al., 2008), and rates of PTSD and disability compensation are rising in veterans (McNally and Frueh, 2013). Many factors underlie this increase in prevalence, including wider recognition of the disorder, widening of the criteria for trauma across iterations of the DSM, reduction in stigma attached to the diagnosis, and an increase in the support available for those affected. However, as awareness and support increase, so do incentives to simulate or exaggerate symptoms.

PTSD is particularly vulnerable to the simulation or exaggeration of symptoms due to the subjective nature of the symptoms reported and because a diagnosis is commonly association with reinforcing personal or financial gains. The simulation or exaggeration of symptoms may take several forms in PTSD; Individuals may unconsciously bias their responses, intentionally produce false or grossly exaggerated symptom profiles, report remitted symptoms as ongoing, or misattribute valid symptoms to a different traumatic event (Kleinman and Stewart, 2004; Knoll and Resnick, 2006; Resnick, 1995). Issues around the reliability of a diagnosis have been exacerbated by a widening of the criteria for the traumatic event required for a diagnosis through iterations of the DSM (Bedard-Gilligan and Zoellner, 2008). In addition, a diagnosis of PTSD, particularly in the military, is often associated with financial and personal gains, including compensation, increased access to medical and support services, avoidance of dangerous work assignments and deferment of or discharge from military service (Denning and Shura, 2017; Guriel and Fremouw, 2003). This problem is not confined to US populations; it has been noted that in German populations symptoms are exaggerated in up to half of all PTSD cases with compensation claims (Maercker, 2009; Stevens and Merten, 2007).

The detection of simulation or exaggeration of PTSD symptoms remains a significant challenge, with potentially high rates of both false positive and false negative identification of malingerers (Guriel and Fremouw, 2003). False positive identification of simulation may occur due to the high levels comorbidity between PTSD and psychiatric and personality disorders (Tanielian et al., 2008). High or diffuse scores of psychopathology and poor symptom discrimination, which are often used to identify

simulation or exaggeration, may be genuine in PTSD (Frueh et al., 2000, 1997). It has been found that distinguishing credible PTSD patients from malingerers based solely on high symptom scores is likely to falsely label combat-related PTSD as simulated (Bagby et al., 1994; Berry et al., 1991). False negative identification of malingering may also occur, as a diagnosis of PTSD is dependent entirely on self-report symptoms, symptom checklists are readily available and the majority of PTSD scales do not include validity checks. In addition, clinicians may be hesitant to diagnose simulation, as a wide range of diagnoses must be ruled out prior to classification, and misclassification may lead to the inability of a valid patient to access necessary care and open the clinician to potential litigation (Burges and McMillan, 2001; Rogers, 2009).

Although the detection of simulation and exaggeration may be challenging, it is of high relevance. The identification and exclusion of individuals with simulated PTSD from valid PTSD populations has important clinical and scientific implications. In clinical settings, lack of treatment efficacy data for combat-related PTSD has been partially attributed to over-reporting of symptoms and reluctance to acknowledge or report therapeutic gains, so that symptoms cannot be accurately measured prior to and following treatment (Guriel and Fremouw, 2003). It has previously been recommended that symptom validity tests (SVT) be included in studies of PTSD (Rosen and Taylor, 2007), that combat-related PTSD subjects enrolled in clinical trials be reported separately from civilian-trauma subjects, and that patients who receive financial benefits or who are awaiting a decision concerning financial benefits based on a continued PTSD diagnosis be excluded from clinical trials (Charney et al., 1998; Freeman et al., 2008).

In addition, research in recent years has investigated the biological mechanisms underlying PTSD. For example, meta-analyses of structural neuroimaging studies of PTSD reveal smaller gray matter volumes in the hippocampus and prefrontal cortex in PTSD patients compared with trauma-exposed non-PTSD or healthy controls (Karl et al., 2006; Kitayama et al., 2005; Kühn and Gallinat, 2013). However, results from individual studies have been inconsistent or contradictory. The importance of seeking to identify and exclude individuals with an unreliable clinical profile when investigating neural differences between PTSD patients and controls is necessary to ensure the robustness of results, and a failure to find reliable or consistent effects may be due in part to unknown levels of heterogeneity between valid patients and malingerers in PTSD populations. However, in the majority of PTSD neuroimaging studies, diagnosis is taken at face validity. In a recent meta-analyses of structural neuroimaging studies of PTSD (Kühn and Gallinat, 2013), none of the 9 studies included reported the use of symptom validity measures. The potential impact of including an unknown number of malingerers along with credible patients in studies of PTSD remains unclear, as no study to date has directly compared these groups. Malingerers may show larger gray matter volumes in regions traditionally found to be reduced in PTSD, thereby weakening results, or they may show differences in regions that are unrelated to PTSD, thereby confounding results.

In the current study, we assess a group of combat-related PTSD patients using structural magnetic resonance imaging (MRI). We distinguish between credible PTSD patients and malingerers using the Morel Emotional Numbing Task (MENT) (Morel, 1998), a two-alternative forced choice test to detect response bias in PTSD (Morel, 1998) that has been shown to have high sensitivity and specificity in detecting symptom

exaggeration (Morel, 2013, 1998). We hypothesize that PTSD patients identified as malingerers will show larger gray matter volumes than credible PTSD patients, in regions previously implicated in PTSD.

2. Methods

2.1. Participants

All participants were male and had been deployed overseas to areas of conflict. Individuals who were voluntarily seeking inpatient psychiatric treatment for combat-related PTSD were recruited and assessed before they began therapy. All participants had experienced the triggering traumatic event within the last 24 months. As inclusion criteria, participants were screened by clinical psychologists and psychiatrists for the presence of mission-related trauma and a current diagnosis of PTSD was made by trained clinicians according to ICD-10 criteria. As exclusion criteria, participants were also screened for current or previous comorbid psychosis or substance abuse, use of psychotropic medication, a history of concussion or traumatic brain injury, neurological symptoms including seizures, and MRI contraindications. The local ethics committee of Charité University Clinic, Berlin, Germany, approved the study and written informed consent was obtained from each participant prior to participation, in line with the declaration of Helsinki. Due to missing MENT data for 15 participants and missing questionnaire data for one participant, a final sample consisting of 46 individuals was included in the analysis. Neuroimaging data was collected at two sites, with a final sample of 9 individuals and 37 individuals from each site respectively. Analysis revealed no significant difference in the distribution of malingerers and credible PTSD patients across sites (see Table 1).

2.2. Questionnaires

To assess PTSD simulation, participants completed the Morel Emotional Numbing Test (MENT). The MENT is a two-alternative forced choice test to detect response bias in

PTSD (Morel, 1998). Participants are asked to match photographs of faces with the appropriate affective labels, for 60 trials. Prior to taking the test, the participant is informed that the ability to recognize emotion is impaired in some individuals with PTSD. However, the test is designed so that individuals without visual or cognitive impairment would achieve near perfect accuracy (Morel, 1998). Malingerers were identified using the cutoff score recommended by the authors, which has been shown to have high overall accuracy (Morel, 1998), as well as high specificity and sensitivity (Morel, 2013). Participants committed on average 4.46 errors (median = 3, SD = 4.74, ranging between 0 and 19).

To assess PTSD symptoms, participants completed the Posttraumatic Diagnostic Scale (PDS) (Foa et al., 1997). The PDS is designed to aid in the diagnosis of PTSD and assess symptom severity. As part of the PDS, respondents rate 17 items representing the main symptoms of PTSD experienced in the past 30 days, on a four-point scale, ranging from 0 ("not at all or only one time") to 3 ("5 or more times a week / almost always").

2.3. Scanning Procedure

Structural images were collected at two sites in Berlin, Germany, using a 3 T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) and a 12-channel radiofrequency head coil. The images were obtained using an identical three-dimensional T1-weighted magnetization prepared gradient-echo sequence (MPRAGE) based on the ADNI protocol (www.adni-info.org; TR = 2500 ms; TE = 4.77 ms; TI = 1100 ms, acquisition matrix = 256 × 256 × 176, flip angle = 7°; 1 × 1 × 1 mm^3 voxel size).

2.4. MRI Data Preprocessing

Structural data were processed with the computational anatomy toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat/) and statistical parametric mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) using default parameters running on MATLAB 9.1 (Mathworks, Sherborn, MA). Voxel based morphometry (VBM) was used to estimate the local gray matter volume (Mechelli et al., 2005). Images were normalized to the Montreal Neurological Institute (MNI) space using the ICBM152 template (Mazziotta et al., 2001) and segmented into gray matter, white matter, and cerebrospinal fluid based on voxel signal intensity and a priori expectations of tissue type based on anatomical location, using default parameters. Modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. Images were smoothed with a full width at half maximum (FWHM) kernel of 8 mm.

2.5. Whole Brain Analysis

A whole-brain voxel-wise factorial analysis was computed. Whole brain analysis allows for unbiased and unconstrained characterization of anatomy, rather than restricting analysis to a priori hypothesized regions of interest (Friston et al., 2006). Age in years, total inter-cranial volume, scanner site, and days of deployment were included as covariates of no interest. An absolute gray matter probability threshold of 0.6 was applied. To control for type-I error, a significant effect was reported when the results met a peak-level threshold of $p < 0.001$ and when the cluster size exceeded the expected voxels per cluster threshold ($k > 83$) in combination with correction for non-isotropic smoothness. The expected voxels per cluster threshold is computed automatically by the

CAT12 toolbox (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) according to random field theory and empirically determines the minimum number of voxels that, in combination with a voxel-level threshold, clusters must meet in order to be reported (Hayasaka and Nichols, 2004). In addition, correction for non-isotropic smoothness adjusts the minimum cluster size depending on the local smoothness of the data. This is a common cluster correction method used for whole-brain analyses in SPM. Coordinate labeling to Brodmann areas was conducted using the online tool BioImage Suite (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html).

2.6. Region of Interest Analysis

We also conducted region of interest (ROI) analysis in the hippocampus, a region consistently found to be smaller in adult PTSD populations (Karl et al., 2006; Kitayama et al., 2005; Kühn and Gallinat, 2013). An anatomical mask for the hippocampus, defined using the anatomical automatic labeling (AAL) (Tzourio-Mazoyer et al., 2002) template and a hippocampal cluster identified in a previous meta-analysis of PTSD whole brain neuroimaging studies (Kühn and Gallinat, 2013) were used. The Region-of-Interest Extraction (REX) Toolbox (Whitfield-Gabrieli, 2009) was used to extract gray matter volumes from the identified clusters.

3. Results

3.1. Participant demographics

From a final sample of 46 patients with combat-related PTSD, we identified 9 malingerers and 37 credible patients, using the MENT and the recommended cutoff score (Morel, 2013, 1998). Comparison of the groups revealed no significant difference in age, number or duration of military deployments, or scanning site (see Table 1). In addition, Fisher's Exact test revealed no significant difference in the rates of secondary psychiatric disorders (see Supplementary Material Table S1) or somatic disorders between credible patients and malingerers.

Table 1. Demographics and questionnaire data.

Variable	Credible PTSD (n = 37)	Malingerers (n = 9)	Test statistic
Age (years)	32.2 (6.3)	32.2 (5.5)	$t(44) = -0.003$, $p = 0.998$
Number of Deployments	2.1 (1.5)	2.6 (2.1)	$t(44) = -0.755$, $p = 0.454$
Days Deployment	323.24 (250.6)	326.1 (209.4)	$t(44) = -0.032$, $p = 0.975$
PDS – Total	31.1 (7.9)	37.8 (9.7)	$t(44) = -2.153$, $p < 0.05$
MENT Errors	2.4 (1.7)	12.8 (4.5)	$t(44) = -11.265$, $p < 0.001$
Scanner Site	6 / 31	2 / 7	$\chi^2(1, N=46) = 0.182$, $p = 0.670$

MENT, Morel Emotional Numbing Test, PDS, Posttraumatic Diagnostic Scale

3.2. PTSD Symptoms

In line with previous work, demonstrating that malingerers display exaggerated symptom profiles (Guriel and Fremouw, 2003), in the current study malingerers reported experiencing significantly more PTSD symptoms than credible patients ($t(44) = -2.153$, $p < 0.05$, see Table 1). PTSD symptoms did not correlate with anatomical ROI hippocampal gray matter volume (credible patients; $r(37) = 0.047$, $p = 0.784$, malingerers; $r(9) = -0.19$, $p = 0.961$) or PTSD meta-analysis ROI hippocampal gray matter volume (credible patients; $r(37) = 0.056$, $p = 0.742$, malingerers; $r(9) = -0.373$, $p = 0.322$).

3.3. Neuroimaging

On the brain structural level, we observed larger gray matter volumes in the malingerer group in both the whole brain and ROI analyses (see Fig. 1). Whole brain analysis revealed larger gray matter volumes in the right hippocampus, right inferior frontal gyrus (IFG) and the right thalamus in the malingerer group ($p < 0.001$, expected voxels per cluster $k > 83$ and non-isotropic smoothness corrected, see Table 2), while no larger gray matter volumes were observed in the credible PTSD group. ROI analysis revealed larger gray matter volume in both the bilateral anatomical hippocampus ($t(44)= 2.504$, $p < 0.05$) and a PTSD specific hippocampal cluster ($t(44)= 2.073$, $p < 0.05$).

Table 2. Whole brain neuroimaging results.

Region	BA	Voxels	MNI			Laterality	t-score
			x	y	z		
Hippocampus	36	202	21	-22	-15	R	3.91
IFG	45	107	46	28	3	R	4.12
Thalamus	50	315	15	-26	4	R	4.07

Corrected at $p < 0.001$ at the voxel level and cluster-extent thresholded at expected voxels per cluster ($k > 83$) in combination with correction for non-isotropic smoothness. BA, Brodmann's Area; IFG, Inferior Frontal Gyrus; MNI; Montreal Neurological Institute, *R, right*

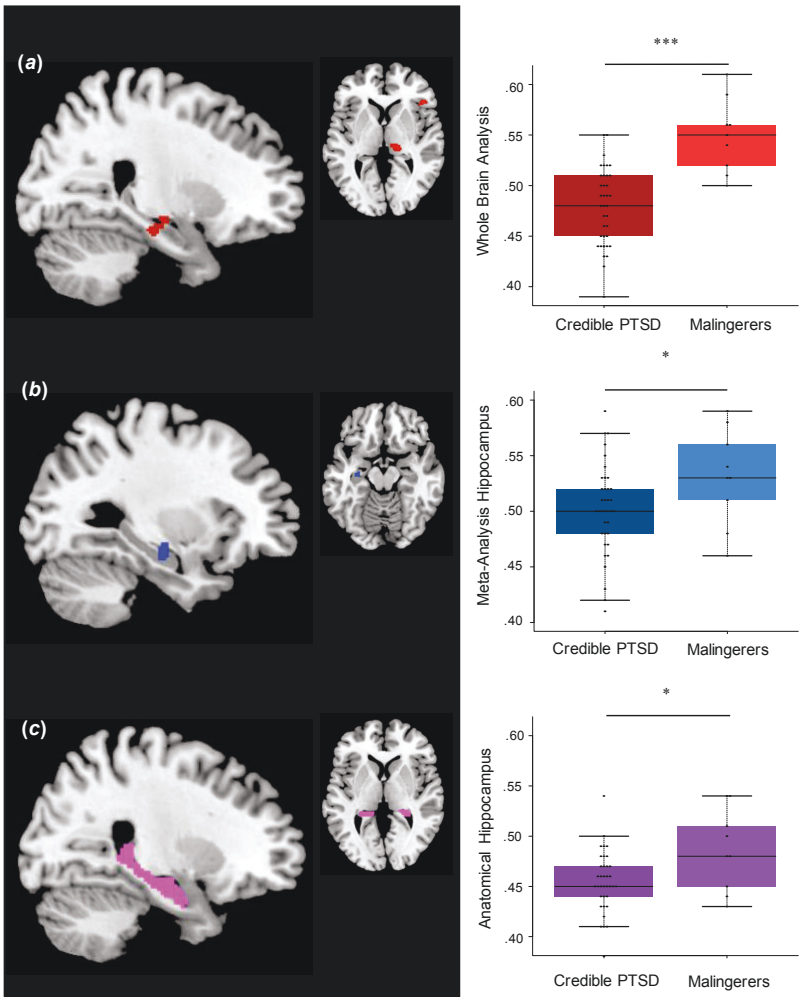

Figure 1. Neuroimaging results.

Larger gray matter volumes were observed in the malingerer group than the credible PTSD group at both the whole brain (a) and region of interest (b & c) levels.

a. clusters in the hippocampus, IFG and thalamus were identified in a whole-brain analysis comparing the simulator and credible PTSD groups ($p < 0.001$, expected voxels per cluster $k > 83$ and non-isotropic smoothness corrected).
b. Hippocampal cluster identified in a meta-analysis of PTSD neuroimaging studies (Kühn and Gallinat, 2013).
c. Bilateral anatomical hippocampus defined using the anatomical automatic labeling (AAL) template (Tzourio-Mazoyer et al., 2002).

Combined box and dot plots display medians, maximums, minimums, interquartile ranges (IQ) and all individual data points separately for the credible PTSD and malingerer groups for the results of the whole brain analysis (a), the hippocampal cluster identified in a meta-analysis of PTSD neuroimaging studies (b) and the bilateral anatomical hippocampus (c). * t-test $p < 0.05$, *** t-test $p < 0.001$

4. Discussion

We compared gray matter volume in PTSD patients classified as malingerers with those classified as credible. As predicted, we observed differences in malingerers at both the whole brain and ROI levels. Malingerers showed higher gray matter volume in the hippocampus, right IFG and thalamus, regions implicated in PTSD symptomatology (Gilbertson et al., 2002), deception (Christ et al., 2009) and response inhibition (Aron, 2007). At a behavioral level, malingerers reported higher PTSD symptoms than credible PTSD patients. This is in-line with a large body of work showing that malingerers often produce exaggerated symptom profiles (Guriel and Fremouw, 2003).

The hippocampus is a key region in learning, memory (Squire, 1992) and fear conditioning (Pohlack et al., 2012) and has commonly been found to be reduced in PTSD populations (Karl et al., 2006; Kitayama et al., 2005; Kühn and Gallinat, 2013). Smaller hippocampal volumes have been related to current PTSD symptomatology (Apfel et al., 2011) and increased risk for PTSD (Gilbertson et al., 2002). The finding of larger hippocampal volumes in the malingerer group may support the hypothesis that these individuals experience fewer symptoms, despite reporting higher symptoms than the credible patient group.

Both the thalamus and the IFG are functionally implicated in deception. A meta-analysis of fMRI neuroimaging studies of deception found that increased activation in the thalamus was related to deception involving recent action events, while activation in the IFG was associated with deception across a wide variety of contexts (Christ et al., 2009). Increased activation in regions including the thalamus and IFG have also been used to correctly differentiate truthful from deceptive responses (Kozel et al., 2005).

Furthermore, the thalamus and IFG are known to play a role in inhibition (Aron, 2007) and attention (Portas et al., 1998; Van der Werf et al., 2003). The IFG has been shown to play a role in general executive function (Hampshire et al., 2010), attention and inhibitory control (Aron et al., 2004). The right IFG has been shown to support inhibition, including cognitive inhibition, response inhibition and inhibition during memory retrieval (Aron, 2007; Aron et al., 2004). Larger gray matter volumes may indicate that malingerers recruit the right IFG to inhibit responses that would reveal their true clinical presentation. In addition, intrusive memories and re-experiencing are one of the key symptoms in PTSD. Malingerers may experience less intrusive memories than valid PTSD patients, although given the subjective nature of these experiences, this is cannot be directly assessed. Given that the right IFG has also been associated with inhibition of memory and suppression of recall, including the inhibition of unwanted memories (Aron et al., 2004), larger IFG volumes in malingerers may indicate that malingerers can more effectively manage or suppress recollections of their traumatic experiences.

We did not observe differences between malingerers and credible PTSD patients in prefrontal regions also commonly found to be reduced in PTSD populations, such as the anterior cingulate cortex (ACC) or the ventromedial prefrontal cortex (vmPFC) (Kühn and Gallinat, 2013). First evidence from twin-studies (Kasai et al., 2008) and more recent work (Butler et al., 2017) suggests that smaller volumes in the ACC and vmPFC in military populations may represent stress-induced loss. In the current study, all participants had experienced combat-related trauma, and there was no difference in duration of military deployment between groups. As such, the current sample may show reduced prefrontal gray matter volumes compared to a non-trauma control group,

although such a sample was not available for the current analysis. Future studies may seek to include a healthy, non-trauma exposed control group to distinguish the neural correlates of PTSD from those of stress exposure in simulated and credible PTSD patient populations.

Malingerers were distinguished from credible PTSD patients using the MENT. Unlike some other SVTs, the MENT does not identify malingerers based on extreme or diffuse measures of psychopathology, and as such should be less likely to misidentify valid combat-related PTSD patients as malingerers. However, despite the reported high sensitivity and specificity of this test (Morel, 2013, 1998), no SVT can distinguish between groups with total accuracy. The authors note that even an error free performance on the MENT cannot definitively rule out simulation or malingering, particularly if the individual suspects they are performing a test of symptom validity. In addition, the reasons underlying an invalid score on a SVT such as the MENT may vary from case to case. Individuals may consciously or unconsciously bias their responses (Kleinman and Stewart, 2004; Knoll and Resnick, 2006; Resnick, 1995), be highly suggestible to the task instructions, or suffer from a neurological impairment or a somatic disorder that may legitimately impair performance. This is particularly relevant when assessing veterans, due to the high prevalence rates of traumatic brain injury (TBI) during military deployment (Taylor et al., 2012), and because combat-related injury is associated with increased risk for PTSD (Hoge et al., 2004; Koren et al., 2005), although in the current sample, individuals with a history of concussion or traumatic brain injury, and neurological symptoms including seizures, were excluded. Future studies investigating the neural correlates of malingering must remain cognizant that neurological, physical

and psychological conditions, such as TBI and somatic symptom disorder, commonly observed in PTSD populations may lead some credible patients to be incorrectly identified as malingerers, and these individuals may also differ at a neural level. One potential solution is to employ a multi-method approach of symptom validity assessment, by including several SVTs, as this has previously been shown to improve detection accuracy (Howe, 2012; Merten et al., 2010). However, the use of multiple SVTs also increases the risk that individuals recognize that they are being assessed for symptom exaggeration and alter their responses accordingly. In a study that employed multiple SVTs, 95% of individuals reported that they believed that one or more of the tests they completed were designed to detect symptom exaggeration, including non-SVTs measures of cognition and PTSD symptoms (Merten et al., 2010). As such, there is no completely accurate method to identify both malingerers and valid PTSD patients (Guriel and Fremouw, 2003) and concerns about increasing detection rates must be balanced against maintaining the validity of individual tests.

One should note that individuals identified as malingerers in the current study had not received a formal clinical diagnosis of malingering. However, a formal, clinical diagnosis of malingering is very rare in PTSD, and the only completely accurate way to establish malingering is if the subject admits to malingering themselves. In the absence of this, a diagnosis of malingering is a probabilistic judgement, made without a clear set of diagnostic criteria, based on clinical interview, symptom validity tests or a combination thereof. However, there is “no evidence that interviews are superior to psychological tests in detecting malingering” (Taylor et al., 2007), and “no method or single instrument that is universally recognized as being the best tool to detect

malingering in PTSD claimants" (Guriel and Fremouw, 2003). In addition, clinicians are often highly reluctant to formally assess or diagnose malingering, due to concerns of angering or alienating the patient by suggesting malingering, or fear of legal action (Guriel and Fremouw, 2003; Taylor et al., 2007). As such, we use the MENT and the cutoff score recommended by the authors to provide "empirically grounded probabilistic evidence of malingering" (Morel et al., 2008) to classify individuals as malingerers. This is in line with the wider literature, as malingerers is the term used both by the authors of the symptom validity test that we used, and by other authors investigating symptom exaggeration based on invalid symptom validity test scores (Guriel & Fremouw, 2003, Spandoni et al., 2015). In addition, the observed brain structural differences between groups in the current sample further supports the use of MENT as a method to distinguish malingerers from credible PTSD patients. However, future studies may seek to combine clinical interviews and symptom validity tests to classify individuals as malingerers.

The generalizability of the current findings may be limited by the population and sample size. In the current sample, 20% of PTSD patients were identified as malingerers. To date, no work has assessed the prevalence of aggravation and simulation in the German military, and as such, it is unclear how representative the current sample is of the wider German military. Given the unequal sample sizes, the analyses may be underpowered to detect smaller effects, and low power may also raise the likelihood of false positives (Button et al., 2013). Future studies should seek to replicate the current findings using equal sample sizes, and explore how these results may extend to non-military and female populations. In addition, prospective studies assessing participants prior to and following therapy may investigate how neural and behavioral changes

following therapy differ between malingerers and credible PTSD patients, as this has important implications for our understanding of treatment efficacy for combat-related PTSD, a condition that has traditionally been shown to have poor long-term outcomes.

In the current study, we compared credible PTSD patients to PTSD patients identified as malingerers and found larger gray matter volumes in the malingerer group in regions implicated in PTSD, inhibition and deception. These results emphasize the need for the inclusion of SVTs in neuroimaging studies of PTSD to ensure that greater validity of PTSD populations, to increase the robustness and consistency of results, and may partly explain inconsistent or contradictory results previously observed in PTSD neuroimaging literature.

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Table S1. Mental and behavioural diagnoses.

ICD-10 Code	Diagnosis	Credible PTSD (n=37)	Malingerers (n=9)	Fisher's Exact Test (2-sided)
F43.1	Post-traumatic stress disorder	37	9	N/A
F10	Alcohol related disorders	5	0	$p = 0.566$
F12.1	Cannabis abuse	1	0	$p = 1.000$
F32.1	Major depressive disorder, single episode, moderate	2	2	$p = 0.167$
F33.2	Major depressive disorder, recurrent severe without psychotic features	2	1	$p = 0.488$
F40.0	Agoraphobia	11	2	$p = 1.000$
F43.2	Adjustment disorders	3	0	$p = 1.000$
F45	Somatoform disorders	2	0	$p = 1.000$
F43.8	Other reactions to severe stress	1	0	$p = 1.000$
F44.8	Other dissociative and conversion disorders	0	1	$p = 0.196$
F63	Impulse disorders	0	1	$p = 0.196$