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BRIEF COMMUNICATION

Treating dissociative post-traumatic stress disorder presenting as a functional movement disorder with transcranial magnetic stimulation targeting the cingulate gyrus

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Abstract

A 29-year-old woman presented with head and neck dystonia, as well as functional seizures. The patient was an active military service member with a history of combat-related trauma. Resting blood oxygen level dependent (BOLD) functional MRI (fMRI) scans of the brain demonstrated an increased anterior cingulate component of the salience network and hyper-connectivity between the insula and cingulate. Following neurological and psychiatric evaluation, she was diagnosed with dissociative post-traumatic stress disorder, partially presenting as a functional movement disorder. Inhibitory repetitive transcranial magnetic stimulation (rTMS) was prescribed with the anterior cingulate as the primary target, and supplementary motor and premotor cortices as secondary targets. The treatment was intended to suppress tremors both directly and indirectly. Thirty-six sessions later, her symptoms were in remission, and she returned to active duty. This case demonstrates the potential efficacy of fMRI-guided rTMS in the treatment of dissociative PTSD.

Keywords Dissociative PTSD · Anterior cingulate · TMS · Functional movement disorder

Introduction

Post-traumatic stress disorder (PTSD) affects approximately 11.1% of the civilian population and 24.5% of veterans [33]. It typically presents as chronic intermittent hyper-arousal accompanied by involuntary repetitive recall of traumatic events. These symptoms are associated with activation in the amygdala, hippocampal formation, and other components of the limbic system [2]. In healthy individuals, the cingulate mediates the aversive response to traumatic stimuli, reducing amygdala activation [19]. It has been suggested that PTSD patients are unable to regulate their fear response due to dysfunction of the anterior cingulate; many even have reduced anterior cingulate cortex volume compared to controls [35]. One prevalent theory proposes that an amygdala-locus coeruleus-anterior cingulate circuit may be responsible for the pathology of this hyper-vigilant form of PTSD. The model postulates that efferent noradrenergic projections out of the locus coeruleus dampen anterior cingulate function, causing the exaggerated emotional and behavioral responses typical of PTSD [10]. PTSD has serious health implications; it is associated with increased risk for chronic musculoskeletal pain, hypertension, hyperlipidaemia, obesity, cardiovascular disease, and suicidality [21, 30].

A small subset of patients (approximately 14.4% based on World Mental Health Surveys) experiences a dissociative subtype of PTSD, which is characterized by an over-suppression of the fear response. Instead of becoming excessively vigilant and anxious, they may experience symptoms related to depersonalization and derealization. Dissociation may be a coping strategy to restrain extreme arousal in PTSD through hyper-inhibition [13]. Nicholson et al. [23] conceptualize this subtype as enhanced top-down regulation of bottom-up fear

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processes. Dissociative PTSD is associated with childhood trauma exposure and comorbid psychiatric disorders such as depression. It is also more likely to affect females and people who do not racially identify as white [34].

Military exposures frequently result in dissociative issues. An analysis of Vietnam War veterans exposed to trauma found that 32% of veterans with PTSD had discrete dissociation. Another study discovered higher levels of dissociation in combat-related PTSD cases than non-combat-related cases; even in subjects without PTSD, combat exposure was associated with more dissociation [26]. Veterans with PTSD already have a worse quality of life than other veterans; they suffer from poorer health, increased disability, and greater functional impairment. Dissociation worsens their outcomes: increased PTSD symptom severity, more drug abuse issues, and additional psychiatric comorbidities. Dissociation is most predictive of functional impairment in veterans and is correlated with worse cognitive performance in memory, attention, and executive function tasks [3].

The dissociative subtype of PTSD has unique neurobiological correlates, mainly in the limbic and prefrontal regions [16]. Trauma reminders are correlated negatively with right anterior insula activation and positively with medial prefrontal and dorsal anterior cingulate cortex activation [17]. Other neuroimaging studies have found increased connectivity between the amygdala and prefrontal regions involved in emotional regulation, as well as between the amygdala and periaqueductal gray, which is involved in fear processing [11, 22]. Daniels et al. [6] also found increased gray matter volume in the right middle frontal gyrus, an area which downregulates emotional arousal, and decreased gray matter volume in the right inferior temporal gyrus, which is involved in visual processing and object recognition. Additional changes related to dissociative episodes occur in the stria terminalis, cerebellum, vestibular nuclei, and other functional associated regions [12, 28, 29].

Many treatments have been attempted to help this relatively refractory group of PTSD patients, including cognitive processing therapy (CPT), prolonged exposure (PE), eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy (NET) [31]. Although exposure-based treatments have proven fairly effective for non-dissociative PTSD, dissociative patients typically end treatment with higher symptom severity and may lose gains [5]. Studies suggest that dissociative pathologies may prevent emotional engagement with trauma-related information, undermining CPT's effectiveness [17, 18]. New options specific to the dissociative PTSD neuropathology are needed.

Transcranial magnetic stimulation may be a promising technique for treating dissociative PTSD considering early successes using TMS to treat classical PTSD patients [24]. Osuch et al. [25] found a greater improvement for hyperarousal symptoms in PTSD patients with rTMS compared with sham, and Kozel et al. [15] corroborated this finding by establishing the superior effectiveness of CPT and rTMS on the right dorsolateral prefrontal cortex as opposed to CPT and sham (sustained up to 6 months afterward). These studies suggest that rTMS may have some applicability to dissociative PTSD as well, though likely with different targets.

Dissociative disorders are frequently accompanied by movement disorders. Unexplained motor symptoms are the most common predecessors to emergency psychiatric admissions for dissociative patients [4]. rTMS has been successfully used to treat functional movement disorders. Although the pathology is unclear and the presentation is heterogeneous, one theory of dystonia asserts that hyperexcitability of the contralateral motor cortex triggers the disorder, which is characterized by sustained abnormal muscle contraction. The application of rTMS on the contralateral premotor cortex and supplementary motor area has been used to reduce motor cortex excitability [1, 20]. As the site of self-initiated voluntary movement, the supplementary motor area has become a common TMS target used to treat movement disorders such as Parkinson's disease [7, 9].

The present case of dissociative PTSD due to military exposure was characterized by a functional movement disorder including torticollis and prolonged recurrent total body clonic spasms. TMS targeting the cingulate, premotor, and supplementary motor cortex was applied in attempts to treat the dissociative PTSD and dystonic movements.

Methodology

Data acquisition

All structural and functional data was acquired on a 1.5 T Siemens Espree scanner with a 16-channel head coil (Erangen, Germany). The structural images were acquired in high spatial resolution in order to properly align subject data to standard atlas space. The structural data was a magnetization-prepared, rapid-acquisition gradient-echo (MPRAGE) T1-weighted sequence (TR = 1810 ms; TE = 3.50 ms; FoV = 180 × 240 mm; resolution 1 mm isotropic). BOLD image acquisitions were 8 min and 20 s long. The functional sequence was acquired while the subject was at rest (TR = 2500 ms; TE = 30 ms; FoV = 192 × 192 mm; resolution 4 mm isotropic; 200 spatial volumes).

Resting BOLD preparation

The fMRI data was cleaned in order to produce interpretable results. Preprocessing was done using tools from the FMRIB Software Library [14, 32, 36]. The skull was de-stripped from the brain; the image was motion corrected and realigned to the middle volume using MCFLIRT; the global mean signal was

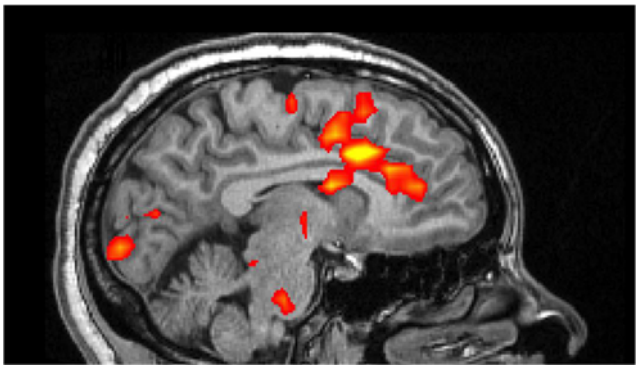

Fig. 1 Functional connectivity map: unilateral insula seed with hyper-connectivity to the anterior cingulate

normalized; and finally it was spatial smoothed with 5 mm FWHM. To further correct for motion artifact, the independent component analysis strategy for automatic removal of motion artifact (ICA-AROMA) was used [27]. A high pass filter was also applied.

Statistical analysis

Functional connectivity, also known as seed analysis, is a method that has been widely implemented to analyze BOLD imaging. It correlates temporal fluctuations in the BOLD signal between a seed of interest and spatially distinct brain regions. This method is used to identify functional relationships between neuroanatomical structures, resulting in a connectivity map. Given the role of the amygdala and insula in mediating anxiety, both were selected, independently and unilaterally, as functional connectivity seeds in order to investigate PTSD networks.

Functional connectivity maps may also be used to differentiate subject groups using group analysis. In the case of this patient, each functional connectivity map was compared with a control groups' corresponding functional connectivity map. The control group consisted of 47 non-psychiatric subjects recruited from Los Angeles Neurology clinics. Subjects with head trauma, neurodegenerative disorders, or psychiatric conditions were excluded. All study procedures were IRB approved and all participants provided written informed consent.

Case description

Patient was a 29 year-old woman and active air force service member with a history of combat-related trauma. She experienced difficulty with a military training course due to a recurring muscle spasm in the right side of the face, as well as limited neck rotation and extension. She also suffered from right arm tremors, body jerks, and on a few occasions, a full body spasm. Symptom onset was triggered by loud alarms sounding. After a particularly acute episode, patient demonstrated slow repetitive speech and global weakness in all four extremities. She experienced persistent muscle spasms in head and neck muscles, predominantly on right side after the incident. She had no history of stroke or seizure disorder (confirmed with EEG). A variety of medications proved ineffective, including clonazepam, Baclofen, Sinemet, Flexeril, and pain medications. Her multi-focal dystonia symptoms persisted without modifying factors or trick maneuvers, except in sleep.

Patient did not report being anxious, and no acute signs of anxiety were apparent, although she was mildly depressed. Her medical imaging study included a T1 structural image, T2 Flair, resting blood oxygen level dependent (BOLD) functional MRI (fMRI), and arterial spin labeling (ASL). The anatomical and ASL images were unremarkable. Although the default mode network appeared normal, the salience network, identified from resting BOLD using independent components analysis, showed hyper-connectivity of the anterior cingulate and insula (Fig. 1). A functional connectivity analysis using unilateral insula as the seed region confirmed hyper-connectivity to the anterior cingulate. Findings were similar for both left and right insula functional connectivity. A seed analysis of the amygdala appeared normal.

Group analysis confirmed hyper-connectivity between the insula and anterior cingulate, as well as minimal contralateral

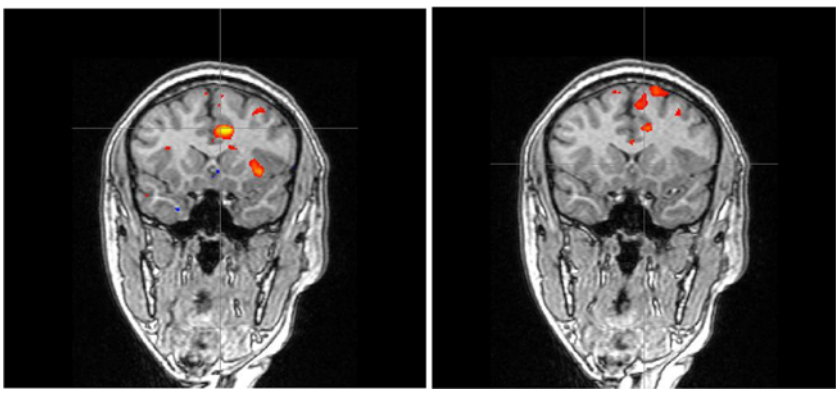

Fig. 2 Statistical functional connectivity map: left and right insula seeds with hyper-connectivity to the anterior cingulate

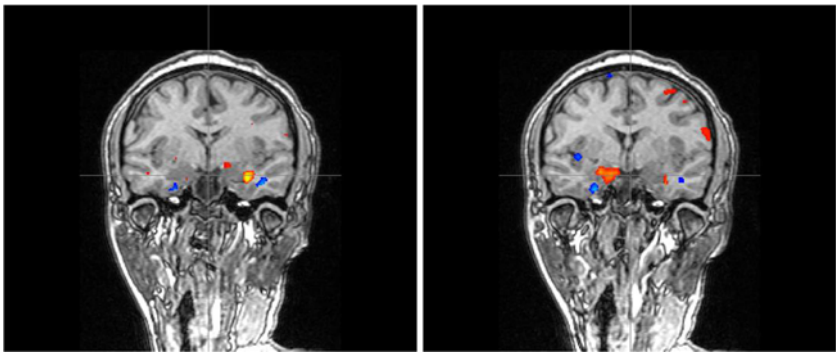

Fig. 3 Statistical functional connectivity map: left and right amygdala seeds with relatively little connectivity to contralateral amygdala

amygdala connectivity. The z-score maps below demonstrate statistically significant unusual connectivity between the insula and anterior cingulate for both the left and right insula seed regions (Fig. 2). We performed the same statistical analysis on the patient's BOLD imaging using the left and right amygdala as seed regions, and confirmed minimal activation in the contralateral amygdala (Fig. 3).

The patient was diagnosed with dissociative PTSD accompanied by functional dystonia. After failing various treatments including psychotherapy, exposure therapy, and counseling, she was prescribed inhibitory rTMS with cingulate as primary target and supplementary motor area (SMA) and premotor cortex (PMC) as secondary targets. She had 36 rTMS sessions at 1 Hz over the course of 2 months: 36 cingulate, 2 PMC (right and left), and 32 supplementary motor area treatments. Treatment led to more articulate speech, reduced motor twitching, and improved mood as recorded by the following questionnaires: Beck Depression Inventory 2 (BDI-2), Generalized Anxiety Disorder 7 (GAD-7), Patient Health Questionnaire 9 (PHQ-9), Beck Anxiety Inventory (BAI), and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (Fig. 4). She reported a Global Rating of Change (GRC) of 1, reflecting a positive improvement. After 36 TMS sessions, she was able to return to active duty.

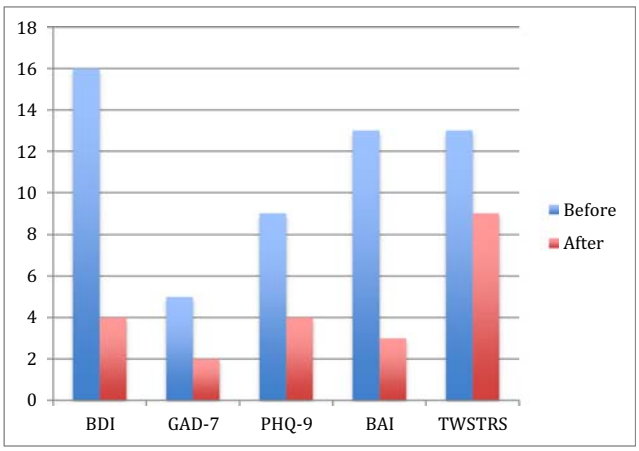

Fig. 4 Questionnaire results: before and after TMS treatment

Discussion

The present case study demonstrates a dissociative form of PTSD with a functional movement disorder. Lack of experiential anxiety and amygdala activation suggested that the patient was suffering from a dissociative subtype of PTSD; this hypothesis was supported by the discovery of hyperconnectivity between the anterior cingulate and insula, which suggests over-suppression of the fear response. Additionally, as a woman of color with military exposure and depression, the patient is in a more high-risk demographic category for dissociative PTSD [34].

The patient was prescribed inhibitory rTMS with the anterior cingulate as the primary target. This treatment aimed to counterbalance the excessive activation of the anterior cingulate seen in her neuroimaging, and by extension, to decrease over-inhibition of the amygdala. She was monitored for any subsequent increase in anxiety, but none occurred. Inhibitory rTMS was also prescribed for the supplementary and premotor motor cortices to help reduce the dystonic symptoms directly by downregulating internally generated movement. Her mood and motor control improved greatly during the course of treatment. After 2 months, her emotional and physical symptoms subsided sufficiently that she was able to return to active duty.

Although the exact mechanisms behind her dystonia remain unclear, Enders et al. [8] suggested that anxiety and dystonia might share common pathophysiological mechanisms, which in this case may have allowed suppressed activation in the amygdala to infect motor processes. Whether this was the result of a direct neurophysiological relationship between anxiety and dystonia, or an indirect relationship mediated by operantly reinforced avoidant behaviors, is uncertain. This phenomenon requires further research.

This case demonstrates the potential power of rTMS to treat dissociative PTSD. To our knowledge, this methodology is novel in the world of dissociative PTSD and presents a useful alternative to therapy-based approaches that do not apply well to this specific subtype. As a case report, this study is limited to a single subject and is not controlled or blinded, which limits generalizability. Further studies are needed to

explore the application of rTMS in dissociative PTSD and more fully validate this treatment technique.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

References

1. Asanuma K, Carbon-Correll M, Eidelberg D (2005) Neuroimaging in human dystonia. J Med Investig 52:272–279
2. Baker D, Risbrough V Behavioral neurobiology of PTSD, Curr Top Behav Neurosci. 38:229–248
3. Boyd J, Protopopescu A, O'Connor C, Neufeld R, Jetly R, Hood H, Lanius R, McKinnon MC (2018) Dissociative symptoms mediate relation between PTSD symptoms and functional impairment in a sample of military members, veterans, and first responders with PTSD. Eur J Psychotraumatol 9(1):1463794
4. Brand B, Myrick A, Sar V, Lanius R (2011) Chapter section 106 psychogenic movement disorders and other conversion disorders trauma and dissociation: clinical manifestations, diagnosis, epidemiology, pathogenesis and treatment. Cambridge University Press
5. Cloitre M, Petkova E, Wang J, Lu F (2012) An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD related to childhood abuse. Depress Anxiety 29(8):709–717
6. Daniels JK, Frewen P, Theberge J, Lanius RA (2016) Structural brain aberrations associated with the dissociative subtype of posttraumatic stress disorder. Acta Psychiatr Scand 133(3):232–240
7. Deiber MP, Honda M, Ibañez V, Sadato N, Hallett M (1999) Mesial motor areas in self-initiated versus externally triggered movements examined with FMRI: effect of movement type and rate. J Neurophysiol 81(6):3065–3077
8. Enders L, Spector JT, Altenmuller E, Schmidt A, Klein C, Jabush HC (2011) Musicians dystonia and comorbid anxiety: two sides of one coin? Mov Disord 26(3):539–542
9. Hamada M, Ugawa Y, Tsuji S (2008) High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord 23(11):1524–1531
10. Hamner MB, Lorberbaum JP, George MS (1999) Potential role of the anterior cingulate cortex in PTSD: review and hypothesis. Depress Anxiety 9(1):1–14
11. Harricharan S, Rabellino D, Frewen PA, Densmore M, Theberge J, McKinnon MC, Schore AN, Lanius RA (2016) fMRI functional connectivity of the periaqueductal gray in PTSD and its dissociative subtype. Brain and Behavior 6(12):e00579. https://doi.org/10.1002/brb3.579
12. Harricharan S, Nicholson AA, Densmore M, Théberge J, McKinnon MC, Neufeld RW, Lanius RA (2017) Sensory overload and imbalance: resting-state vestibular connectivity in PTSD and its dissociative subtype. Neuropsychologia 106:169–178
13. Huijstee J, Vermetten E (2017) The dissociative subtype of posttraumatic stress disorder: research update on clinical and neurobiological features. In: Vermetten E
14. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM (2012) FSL. NeuroImage 62(2):782–790
15. Kozel FA, Motes MA, Didehbani N, DeLaRosa B, Bass C, Schraufnagel CD, Jones P, Morgan CR, Spence JS, Kraut MA, Hart J Jr (2018) Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: a randomized clinical trial. J Affect Disord 229:506–514
16. Lanius RA, Williamson PC, Boksman K, Densmore M, Gupta M, Neufeld RW et al (2002) Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. Biol Psychiatry 52(4):305–311
17. Lanius RA, Vermetten E, Loewenstein RJ, Brand B, Schmahl C, Bremner JD, Spiegel D (2010) Emotion dysregulation in PTSD: neurobiological and clinical evidence for a dissociative subtype. Am J Psychiatry 167(6):640–647
18. Laycox LH, Foa EB, Morral AR (1998) Influence of emotional engagement and habituation on exposure therapy for PTSD. J Consult Clin Psychol 66(1):185–192
19. Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, Koeppe RA, Fig LM (1999) Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry 45(7):817–826
20. Lozeron P, Poujois A, Richard A, Masmoudi S, Meppiel E, Woimont F, Kubis N (2016) Contribution of TMS and rTMS in the understanding of the pathophysiology and in the treatment of dystonia. Front Neural Circuits 10:90. https://doi.org/10.3389/fncir.2016.00090
21. McFarlane AC (2010) The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry 9(1):3–10
22. Nicholson AA, Densmore M, Frewen PA, Theberge J, Neufeld RW, McKinnonc MC, Lanius RA (2015) The dissociative subtype of posttraumatic stress disorder: unique resting-state functional connectivity of basolateral and centromedial amygdala complexes. Neuropsychopharmacology 40(10):2317–2326
23. Nicholson AA, Friston KJ, Zieidman P, Harricharan S, McKinnon MC, Densmore M et al (2017) Dynamic causal modeling in PTSD and its dissociative subtype: bottom-up versus top-down processing within fear and emotion regulation circuitry. Hum Brain Mapp 38(11):5551–5561
24. Novakovic V, Sher L, Kyle AB, Mindes J, Golier JA, Yehuda R (2011) Brain stimulation in posttraumatic stress disorder. Eur J Psychotraumatol 2(1):5609
25. Osuch EA, Benson BE, Luckenbaugh DA, Geraci M, Post RM, McCann U (2009) Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. J Anxiety Disord 23(1):54–59
26. Özdemir B, Celik C, Oznur T (2015) Assessment of dissociation among combat-exposed soldiers with and without posttraumatic stress disorder. Eur J Psychotraumatol 6:26657
27. Pruim RHR, Mennes M, Buitelaar JK, Beckmann CF (2015) Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. NeuroImage 112:278–287
28. Rabellino D, Densmore M, Harricharan S, Jean T, McKinnon MC, Lanius RA (2018a) Resting-state functional connectivity of the bed nucleus of the stria terminalis in post-traumatic stress disorder and its dissociative subtype. Hum Brain Mapp 39(3):1367–1379
29. Rabellino D, Densmore M, Théberge J, McKinnon MC, Lanius RA (2018b) The cerebellum after trauma: resting-state functional connectivity of the cerebellum in posttraumatic stress disorder and its dissociative subtype. Hum Brain Mapp 39(8):3354–3374
30. Ramsawh HJ, Fullerton CS, Mash HB, Ng TH, Kessler RC, Stein MB, Ursano RJ (2014) Risk for suicidal behaviors associated with PTSD, depression, and their comorbidity in the U.S. Army. J Affect Disord 161:116–122

31. Schiavone FL, Frewen P, McKinnon M, Lanius RA (2018) The dissociative subtype of PTSD: an update of the literature. PTSD Research Quarterly: National Center for PTSD 29(3)
32. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H et al (2004) Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 23:208–219
33. Spottswood M, Davydow DS, Huang H (2017) The prevalence of posttraumatic stress disorder in primary care: a systematic review. Harv Rev Psychiatry 25(4):159–169
34. Wolf EJ, Lunney CA, Miller MW, Resick PA, Friedman MJ, Schnurr PP (2012) The dissociative subtype of PTSD: a replication and extension. Depress Anxiety 29(8):679–688
35. Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S (2006) Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry 59(7):582–587
36. Woolrich MW, Jbabdi S, Patenaude B, Chapell M, Makni S, Behrens T et al (2009) Bayesian analysis of neuroimaging data in FSL. NeuroImage 45:173–186

We attest that the manuscript has not been published previously and is not under consideration for publication elsewhere. Co-authors contributed significantly to the manuscript and have consented to be listed as co-authors. Sheldon Jordan, as the lead investigator, takes full responsibility for the data, analyses, interpretation, and the conduct of the research. He has full access to all the data and the right to publish any and all data related to this project. In the manuscript, we provide accurate reporting of participant informed consent.