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Author

Koek, Ralph Jan

Publication Date

2024-05-01

Data Availability

The data associated with this publication are in the supplemental files.

Peer reviewed

Deep brain stimulation of the amygdala for treatment-resistant combat post-traumatic stress disorder: Long-term results☆

Ralph J. Koek [a,b,*], Josue Avecillas-Chasin [c], Scott E. Krahl [d,e], James WY. Chen [f,g], David L. Sultzer [a,h], Alexis D. Kulick [i], Mark A. Mandelkern [j], Maura Malpetti [k], Hailey L. Gordon [l], Holly N. Landry [m], Evan H. Einstein [a], Jean-Philippe Langevin [n,o]

[a] Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at University of California, Los Angeles, 760 Westwood Blvd., Room 58-229, Los Angeles, CA, USA, 90095-1759
[b] Psychiatry Service, Mental Health and Behavioral Sciences, Sepulveda Ambulatory Care Center, VAGLAHS, 16111 Plummer St. (116A-11), North Hills, CA, USA, 91343
[c] Department of Neurosurgery University of Nebraska Medical Center College of Medicine, 42nd and Emile, Omaha, Nebraska USA, 68198
[d] Department of Neurosurgery, University of California at Los Angeles (UCLA), 300 Stein Plaza Driveway Suite 420, Los Angeles, CA, 90095, USA
[e] Research Service, VAGLAHS (Clinical Neurophysiology), 16111 Plummer St., Building 1, North Hills, CA, USA, 91343
[f] Department of Neurology, UCLA, 710 Westwood Plaza, Los Angeles, CA, 90095, USA
[g] Neurology Service (Epilepsy Center of Excellence), VAGLAHS, 11301 Wilshire Blvd, Los Angeles, CA, USA, 90073
[h] Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine Institute for Memory Impairments and Neurological Disorders, 3214 Biological Sciences III, Irvine, CA, USA, 92697-4545
[i] Psychology Service (Neuropsychology), Mental Health and Behavioral Sciences, VAGLAHS, 16111 Plummer St. (116A-11) North Hills, CA, USA, 91343
[j] Imaging Department, VAGLAHS, 11301 Wilshire Blvd, Los Angeles, CA, USA, 90073
[k] Department of Clinical Neurosciences, Cambridge University Hospitals NHS Trust, University of Cambridge, Cambridge, UK
[l] STEM Pathways at Boston University, 610 Commonwealth Avenue, Room 402, Boston, MA, 02215, USA
[m] Private Practice at Happier Living, USA
[n] Department of Neurosurgery, UCLA, 300 Stein Plaza Driveway Suite 420, Los Angeles, CA, 90095, USA
[o] Southwest VA Epilepsy Center of Excellence, 11301 Wilshire Blvd, Bldg 500 (10H2), Los Angeles, CA, USA, 90073

ARTICLE INFO

ABSTRACT

Deep brain stimulation (DBS) holds promise for neuropsychiatric conditions where imbalance in network activity contributes to symptoms. Treatment-resistant Combat post-traumatic stress disorder (TR-PTSD) is a highly morbid condition and 50% of PTSD sufferers fail to recover despite psychotherapy or pharmacotherapy. Reminder-triggered symptoms may arise from inadequate top-down ventromedial prefrontal cortex (vmPFC) control of amygdala reactivity. Here, we report long-term data on two TR-PTSD participants from an investigation utilizing high-frequency amygdala DBS. The two combat veterans were implanted bilaterally with quadripolar electrodes targeting the basolateral amygdala. Following a randomized staggered onset, patients received stimulation with adjustments based on PTSD symptom severity for four years while psychiatric and neuropsychiatric symptoms, neuropsychological performance, and electroencephalography were systematically monitored. Evaluation of vmPFC-Amygdala network engagement was assessed with ^{18}FDG positron emission tomography (PET). CAPS-IV scores varied over time, but improved 55% from 119 at baseline to 53 at 4-year study endpoint in participant 1; and 44%, from 68 to 38 in participant 2. Thereafter, during 5 and 1.5 years of subsequent clinical care respectively, long-term bilateral amygdala DBS was associated with additional, clinically significant symptomatic and functional improvement. There were no serious stimulation-related adverse psychiatric, neuropsychiatric, neuropsychological, neurological, or neurosurgical effects. In one subject, symptomatic improvement was associated with an intensity-dependent reduction in amygdala theta frequency power. In our two participants, FDG-PET findings were inconclusive regarding the hypothesized

mechanism of suppression of amygdala hyperactivity. Our findings encourage further research to confirm and extend our preliminary observations.

1. Introduction

Post-traumatic stress disorder (PTSD) has a lifetime prevalence of up to 27% among Iraq and Afghanistan combat veterans (Harpaz-Rotem and Hoff, 2015). Individual trauma-focused cognitive-behavior therapy (TF-CBT) and medications (paroxetine, sertraline and venlafaxine) are effective treatments (VA/DoD 2023). However, more than half of combat PTSD patients still meet diagnostic criteria for PTSD after treatment (Steenkamp et al., 2020) or 6 months later (Levi et al., 2022). Lower effect sizes and increased dropout rates with TF-CBT are seen among veterans compared with other populations (Kitchiner et al., 2019). There is a dearth of evidence on next best treatment choices for individuals who fail to benefit from standard treatments, i.e., those with treatment-resistant PTSD (TR-PTSD) (Koek et al., 2016; Sippel et al., 2018). Chronic PTSD leads to severe emotional suffering, lower quality of life, worsened physical health, accelerated epigenetic aging (Na et al., 2022), increased cardiovascular disease morbidity (O'Donnell et al., 2021) and risk for suicide (VA/DoD 2023).

Failure to extinguish fear resulting from insufficient ventromedial prefrontal cortex (vmPFC) inhibition of basolateral amygdala (BLA) activity is a central feature of PTSD treatment resistance (van Rooij et al., 2021). Unopposed activity of the BLA may lead to pervasive fear and exaggerated "fight or flight" responses to trauma reminders. Higher pre-treatment BLA activity has been a predictor of treatment failure in many (e.g., van Rooij et al., 2016; Fonzo et al., 2017; Hinojosa et al., 2023) although not all (e.g., Joshi et al., 2020) studies; amygdala hyperactivity and vmPFC hypoactivity characterize untreated PTSD, particularly in association with trauma reminders (Etkin and Wager, 2007; Hayes et al., 2012). Treatment response is associated with improved vmPFC vs Amygdala activity balance (Zhu et al., 2018) which may suggest a basis for DBS treatment of PTSD (Meeres and Hariz, 2022; Becker and Milad, 2023). Given these findings and the results of our pre-clinical study (Langevin et al., 2010), we initiated a pilot study using deep brain stimulation (DBS) designed to focally and functionally reduce amygdala activity to facilitate fear extinction in combat veterans with TR-PTSD (Koek et al., 2014). We previously reported findings at 8 months in our first subject (Langevin et al. 2016a, 2016b). Here, we present detailed long-term clinical outcomes of two subjects in relation to network engagement as evidenced by neuroimaging findings and electrophysiological data.

2. Method

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The protocol (NCT02091843; FDA IDE #G120095) was approved by the VA Greater Los Angeles Institutional Review Board. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. Subjects met criteria for Stage II TR-PTSD (Sippel et al., 2018). Prior treatment history is included in Supplementary data. doc. We planned to study 6 men with combat PTSD, but were able to recruit only two as of the time of this report, which includes the results from their completion of a 4-year trial and subsequent open-label clinical follow-up. Recruitment challenges included limited number of veterans who had tried and failed evidence-based psychotherapy, reluctance to undergo surgery, loss of initial trial funding, and limited clinician referrals (see Supplementary data. doc for recruitment history and CONSORT diagram).

Participants were implanted with quadripolar electrodes (Medtronic 3387[R]) within the BLA (Langevin et al., 2016a; Avecillas-Chasin et al., 2019; Lai et al., 2020). Stimulation adjustments were guided by symptom severity measured with the DSM-IV Clinician Administered PTSD

Rating Scale (CAPS-IV) (Blake et al., 1995). One month after surgery with stimulators kept off, participants underwent all-day EEG telemetry during which stimulation settings were systematically tested for safety and potential efficacy (ie., stimulation mapping session; Lai et al., 2020). Then, they were randomized in a 1:1 block design fashion to 2 (participant 1) or 3 (participant 2) months of sham vs active stimulation at the lowest setting that was tolerated and beneficial during EEG telemetry. We called this "month 0." Findings from the double-blind sham period were unblinded for this manuscript. Informed by our preclinical study (Langevin et al., 2010) and stimulation mapping session (Lai et al., 2020), we used monopolar stimulation in the bilateral BLA at 160 Hz. Pulse width was kept at 60 *us* throughout the trial except for 90 us in participant 2 during the first month of the sham-controlled period (see below). A 30% reduction in CAPS-IV Total score was our *a priori* definition of treatment response. Stimulation was adjunctive to psychotherapy, pharmacotherapy and psychosocial interventions provided by the participant's usual care team. Participant ratings of PTSD severity were measured with the DSM-IV-based Davidson Trauma Scale (DTS) (Davidson et al., 1997).

At baseline, monthly for 15 months, and then quarterly for 33 months, the following outcome measures were administered.

(1) CAPS-IV (Primary outcome measure) and DTS.
(2) Depression, generalized anxiety, mania, suicidal ideation and behavior, cognition and functioning using validated measures (Detailed in Koek et al., 2014).
(3) Systematic assessment for abnormalities in emotional social perceptions potentially seen in individuals with amygdala damage, including validated measures and a screening instrument developed for this study called the Amygdala Related Behavioral Change inventory (Koek et al., 2014).
(4) Resting 1-h EEG with stimulation turned off.

At 6, 24 and 48 months, a neuropsychological battery comprising measures of attention, working memory, verbal and non-verbal memory, language, visuospatial, and executive functions typically associated with frontal-subcortical circuits was administered.

Quantitative results of all measures are provided in Supplementary data. xlsx. Verbal descriptions of participant progress in relation to stimulation changes are provided in Supplementary data. doc.

2.1. Imaging design and data acquisition

Participants underwent resting and provocative PET scans using [18F]2-fluoro-2-deoxy-D-glucose (FDG) to determine the relative metabolic activity of the amygdala, hippocampus, insula, and vmPFC, both prior to and after surgical intervention. After intravenous injection with approximately 5 mCi of FDG, participants underwent a 60 min uptake period followed by a 20 min scan in a Siemens mCT PETCT scanner, with axial slice thickness of 2.0 mm and spatial resolution of 4.1 mm FWHM (Jakoby et al., 2011). During the uptake period they were either resting quietly in a dimly lit room or exposed to a provocation, consisting of an "exposure" session with the study psychiatrist. This session consists of re-exposure of the veteran to the initial trauma that caused PTSD, using the CAPS-IV interview (Blake et al., 1995) including detailed review of Criterion A. The CAPS-IV was chosen because it facilitated trauma-related hyperarousal throughout the 60-min FDG uptake period, typically comparable to the duration of flashbacks experienced by our combat veterans with TR-PTSD. The resting scan was performed a day before the exposure session as a baseline (resting condition). The provocative scan was performed to target brain metabolism in a

symptomatic phase. Both scans were repeated post-operatively 16.3 ± 0.96 months later. We acquired 3D T1-weighted MPRAGE images, with and without contrast, in a Siemens 3 T scanner, with axial slice orientation and slice thickness of 1.0 mm. We collected the data of 11 healthy subjects (all male with a mean age 57 years, SD 3.3 years), including FDG-PET and T1-MRI images and Freesurfer segmentation data, as described in LaMontagne et al. (2019) (freely available OASIS repository (http://www.oasis-brains.org)). These control subjects received an

intravenous injection of 5 mCi of FDG immediately followed by a dynamic 60 min PET acquisition, with an effective resolution of 5 mm FWHM. We compared the final 20 min of their PET scans with those of our participants. Each participant's T1-weighted MRI image was segmented and parcellated using FreeSurfer v.6.0, with additional brainstem and amygdala segmentation, to define volumes of interest (VOI). The FDG-PET images were reoriented and co-registered to corresponding MRI images in native space using SPM12. Standardized
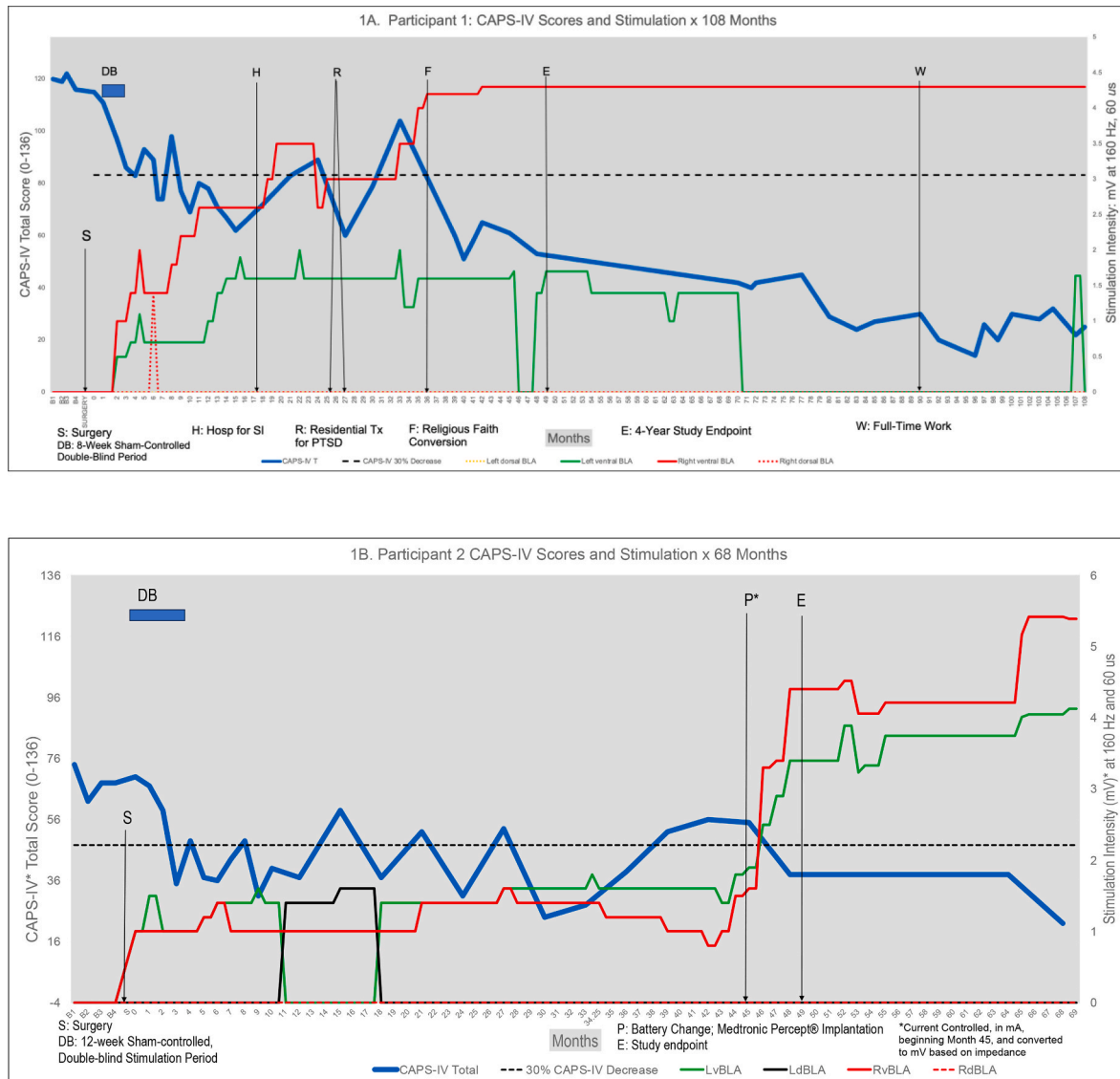

Fig. 1. Amygdala DBS for PTSD: CAPS Scores and Stimulation Adjustments

Fig. 1 Legend: Bilateral, continuous Deep Brain Stimulation of the basolateral amygdala (BLA), targeting either right (R) or left (L) dorsal (dBLA) or ventral (vBLA) contacts located within that structure. Stimulation intensity is shown in volts. Frequency was kept at 160 Hz except for a 1-month unsuccessful trial of 100 Hz at month 25 in participant 1. Pulse width was kept at 60*us*, except for a 1-month trial from Month 0 to Month 1 in participant 2 during the double-blind period (see text). Stimulation was monopolar with case (+). B = Baseline, with 3 CAPS-IV measures over 3 months in participant 1 and 4 measures over 6-months (due to delay in surgery scheduling availability) in participant 2: participant 1 CAPS-IV mean 119 (s.d. 2.5); participant 2, CAPS-IV mean 68 (s.d. 4.9) prior to surgery. Months on X-Axis are from date of surgery, with "Month 0," being 1-month after surgery, when double-blind active-vs-sham stimulation began. Some dates of CAPS assessment occurred at intervals other than monthly due to scheduling difficulty, and some stimulation intensity changes occurred between months for the same reason. A 30% reduction in CAPS-IV total score was the *a priori* designation of responder status, based on data available at time of study initiation. Beginning at month 49, patients were seen for clinical care and subsequently symptom measurement was not systematic. The last recorded CAPS-IV rating in participant 1 was at month 83. Thereafter, only the CAPS-5 was used. Clinicians for participant 2 did not record symptom measures for over a year after study completion. Beginning at month 103 in participant 1, and 63 in participant 2, CAPS-5 scores were recorded prospectively. To permit comparison of symptom severity across the entire period of observation, CAPS-5 scores were converted to imputed CAPS-IV scores by multiplying the 17 items both scales have in common by two (see Supplementary data. doc for reference). Participant 1 had Medtronic[R] Activa PC[R] pulse generator battery replacement at month 55. Participant 2 had Medtronic[R] Activa PC[R] pulse generator replaced with Medtronic[R] Percept™ at month 45.5. Participant 1 had Medtronic[R] Percept™ placed at Month 93. During month 107 in participant 1, L vBLA was added inadvertently for 3 weeks, without exacerbation of PTSD.

uptake value ratios (SUVr) values for amygdala, hippocampus, insula and vmPFC were obtained by dividing the mean FDG-PET activity in corresponding VOI by that of the pons. We hypothesized that pre-stimulation, the scan conducted during trauma reminder, compared to the scan at rest, would be associated with increased amygdala and/or insula metabolism but not vmPFC metabolism. After 1 year of amygdala DBS, we predicted that there would be less provocation-induced increase in amygdala and/or insula metabolism.

After the 4-year trial, both participants continued psychiatric care at the VA Greater Los Angeles, receiving both medications and psychotherapy while DBS was managed by study investigators based on participant reports and treating clinician descriptions of PTSD symptoms. Six months prior to the time of submission, the VAGLAHS IRB approved, and both participants consented to, retrospective collection of clinical data for research, and ongoing measurement of PTSD symptom severity with the CAPS-5 (Weathers et al., 2018) and PCL-5 (Bovin et al., 2016). Clinical ratings done during open-label follow-up with the CAPS-5 and PCL-5 were converted to CAPS-IV equivalent scores using imputation (iCAPS-IV), by totaling the 17 items of the CAPS-5 also found in CAPS-IV and multiplying by two (see Supplementary data. doc for details).

3. Results

3.1. PTSD outcome

Relationships between symptoms and setting changes are detailed in Fig. 1 pdf and Supplementary data. xlsx and. doc. Participant-rated PTSD severity ratings with the DTS paralleled the CAPS-IV, but were typically higher, as found by others using DSM-5 scales (Resick et al., 2023).

The first participant, a 48-year-old male (sex assigned at birth) tank gunner with extremely severe TR-PTSD and both dissociative and psychotic features at baseline (CAPS-IV 119/136), was previously described (Langevin et al., 2016a). He completed the 4-year study protocol and 5 subsequent years of clinical follow-up (Fig. 1A pdf). He was initially randomized to sham stimulation for two months, during which his total CAPS-IV score improved from baseline of 119 to 111 after 1 month, and 97 after two months. Severe re-experiencing, including terrifying nightmares, flashbacks and hyperarousal; visual, auditory and somatosensory hallucinations of long-standing; and trauma reminder-triggered dissociative episodes similar to baseline (Supplementary baseline video. mp4) persisted. Open label, monopolar (Case +) stimulation at 1 V (V) Right (R) and 0.5 V Left (L) ventral BLA (vBLA) contacts began after 2 months. The first day of active stimulation, he reported improved mood and exhibited objective calming. A week later, he reported feeling "better than good," without hypomania. Over the next 7–8 months, nightmares and dissociation progressively resolved with stimulation adjustments to 1.4 V R vBLA and 0.7 V L vBLA (Langevin et al., 2016a). Persistent symptoms led to further stimulation adjustments to 2.6 V R vBLA and 1.6 V L vBLA at month 15, when CAPS-IV score was reduced to 62, a 48% improvement from baseline. The participant then took his second international trip since study enrollment (having been unable to travel due to PTSD for many years prior to enrollment). A month later, he quit his job because he realized the customer service work was not his passion. Thereafter he became depressed, requiring a 7-day hospitalization for suicidal ideation during month 17. Subsequently, additional outpatient psychotherapy, medication adjustments, and a residential PTSD treatment program were provided, in addition to stimulation adjustments, with variable improvement until month 36. Then, after stimulation was increased to 4.2 V R vBLA and 1.6 L vBLA, PTSD symptoms improved to >40 % reduction in CAPS-IV from baseline. He maintained that degree of improvement for the last year of the trial.

After trial completion, the same stimulation settings were continued. At month 54, unexpected clinical deterioration led to discovery of battery depletion. There was rapid recovery after battery replacement.

Thereafter, he remained significantly improved but requested stimulation adjustments to address persistent symptoms unrelated to combat experience, consisting of brief reliving of past experiences fulfilling criteria for *deja vecu*. Increases and decreases in both left and right vBLA stimulation, and one trial of bipolar stimulation at R vBLA (4.3 V, 9-, 10+; L vBLA monopolar at 1.4 V) were either not tolerated or not beneficial. At month 70, stimulation was changed to unilateral 4.3 V R vBLA and 2 weeks later he reported 40% reduction in *deja* vecu and other intrusive symptoms, and significant calming. The DTS score decreased from 67 to 52. At month 66, he described intrusive recollections of a never previously reported childhood trauma. He believed that reduction in combat PTSD symptoms allowed "leaking" of these memories into consciousness. He eventually accepted a referral for psychotherapy. From months 74–76 he received Eye Movement Desensitization and Reprocessing therapy (EMDR) with initially increased symptom severity (CAPS-IV 45; DTS 68) at month 77, but subsequent improvement (CAPS-IV 29 and DTS 51) at month 80. From month 70 onward, R unilateral stimulation was overall associated with progressive symptomatic improvement and eventual recovery: from month 83–108, CAPS-5 ranged from 9 to 17 (Fig. 1A pdf; iCAPS-IV 14–32), and PCL-5 from 27 to 35 (Supplementary data. xlsx).

Clinically, the relief of severe combat nightmares, which occurred 3–7 times weekly for decades prior to DBS, a mean of 14 nights/month during the first 8 months of DBS, and only 9 times in >8 subsequent years of DBS, has been profoundly valuable. Resolution of severe dissociative episodes, another dramatic benefit, has persisted from month 8 to present (Supplementary 4-Year video. mp4). There was little change in trauma-related contamination obsessive-compulsive symptoms (Supplementary data. doc) through month 48, nor after completion of exposure and response prevention CBT from months 49–54, but this substantially improved in years 8–9. Functional improvements over 9 years of DBS include re-engagement with family and peers; overseas travel for both work and pleasure; college graduation; and successful full-time employment in a new career.

The second participant, a 39-year-old male (sex assigned at birth), enrolled because of treatment-resistant difficulty with anger expression in the context of PTSD. He developed PTSD after extensive combat experiences in Iraq. His baseline CAPS-IV of 68 encompassed nightmares, flashbacks, constant hypervigilance, and impulsive aggression leading to severe avoidance. Despite extensive pharmacotherapy and psychotherapy, and multidisciplinary rehabilitation for co-morbid physical conditions including traumatic brain injury and chronic headaches, his loud, menacing and occasionally violent anger expression led to divorce, estrangement from family, and inability to work. Prior to enrollment, we conducted a chart review and interviews of the participant, family and clinicians to catalogue clinically significant dysfunctional anger expression events, divided into three subtypes: 1) Violence (VL): physically harming another person during impulsive anger; 2) Intervention (IN): Anger expression toward others leading to police or security intervention to prevent violence; and 3) Verbal (VE): Anger expression leading to disruption of an important social engagement or relationship. (See Supplementary data. doc for examples). During 28 months of available documentation prior to enrollment, there were 4 V L, 8 IN and 13 VE acts (Total = 0.89/month). During the 48-month trial, there were 0 V L, 6 IN, and 19 VE events (0.52/month). In 18 months of clinical follow-up since study completion, two VE, and one VL incident (0.17/ month) have occurred (Fig. 2 pdf). Improved anger control has allowed participant 2 to rekindle family relationships, engage in romantic relationships, resume recreational activities, and successfully raise a teenager as a single father. Family members and treating clinicians have repeatedly reported improved control of anger expression. His overall CAPS-IV score showed variable improvement (Fig. 1B pdf), with triggered exacerbations of nightmares, flashbacks, and persistent hypervigilance. In the last 3 months of the study and over the 18 months since study completion, PTSD symptoms improved with stimulation increases (Fig. 1B pdf) based on intracranial recording (see below).
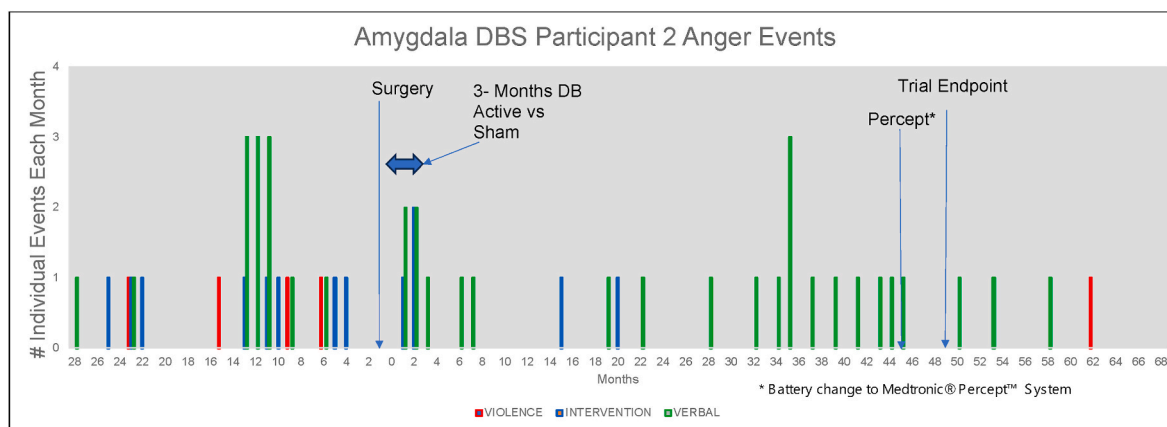
Fig. 2. Participant 2 Anger Events
Fig. 2 Legend: See text for definition of the three types of anger events. Events were determined from review of records and interviews of participant, family members, and treating clinicians for the 28-month period prior to enrollment, and thereafter, monitored prospectively. (The veteran had dropped out of care for over a year prior to returning, 28 months prior to enrollment).

Participant 2 was initially randomized to active stimulation. Both reexperiencing and anger worsened during the first month, with two IN events at 1.0 V L vBLA +1.0 V R vBLA, 90 *u*S, 160 Hz. There was further worsening at 1.5 V L vBLA +1.0 V R vBLA 90 *u*S, 160 Hz, including 2 additional IN events in two weeks. When stimulation was changed to 1.5 V L vBLA, 1.0 V R vBLA, 60 *u*S, 160 Hz, there were two more VE events in the next 2 weeks, and persistent reexperiencing. After stimulation change to 1.0 V vBLA bilaterally, within a few days the participant, his treating clinicians and his family described significant improvement. This persisted for 9 months. He began volunteering at his daughter's high school and resumed bowling. The CAPS-IV was reduced to 35 from a peak of 70 during the double-blind period. Over the next year improvements in anger control and avoidance persisted, with only two VE incidents, although reexperiencing symptoms did not improve. Stimulation adjustments were attempted, but intensity above 2 V was not tolerated. Participant 2's pulse generator battery expired at month 45 and was replaced with the Medtronic[R] Percept™. Thereafter, stimulation intensity was raised gradually to 3 milli-amperes bilaterally (3.4 V L vBLA and 4.4 V R vBLA) targeting BLA theta (6.9 Hz), with progressive symptom improvement as of month 48 (CAPS-IV 38; DTS 49). In year 5, there were two VE incidents, and reported stability of other PTSD symptoms, although no quantitative measures of PTSD severity were documented. At month 62 there was a VL incident. This was not associated with worsened PTSD symptoms. It occurred in the context of medication non-adherence (divalproex and venlafaxine) and losing his mother to cancer. The DBS system was found to be operating normally, and there were no neurologic or neuropsychiatric changes. He had markedly altered his diet, leading to a hospitalization for acute pancreatitis a month after the anger incident. Since then, his diet has normalized and he has discontinued divalproex. With modest stimulation increase, there have been no other anger incidents and overall PTSD symptoms are very much improved. At month 63, PCL-5 score was 28, at month 64 it was 23, and at month 67, 14. CAPS-5 scores were 23 and 14 at months 64 and 67 (iCAPS-IV 38 and 22, respectively).

3.2. Adverse events

Chronic amygdala DBS was not associated with serious adverse effects attributable to stimulation. There was one serious adverse event felt to be due to the underlying illness: Participant 1 required hospitalization for suicidal ideation after reaching 48% CAPS-IV reduction during month 17. Comprehensive assessment revealed no clear relationship to stimulation and no intercurrent medical conditions or social stressors. He recovered after a 6-day hospitalization without stimulation change. There were similar episodes with hospitalization 4, 9 and 19

years before study enrollment. The study team and treating clinicians concluded that the emotional burden of recovery from severe chronic impairment, combined with persistent PTSD-related moral injury (Wisco et al., 2017) were likely responsible. Moral injury symptoms improved after month 36 when stimulation intensity was increased (see above) and the participant simultaneously described a deepened spiritual connection.

Surveillance EEGs showed no after-discharges or epileptiform activity (Langevin et al., 2016b). Systematic monitoring has revealed no clinically significant perceptual, behavioral or personality changes, nor emergence of clinical depression or mania. There were occasional reversible, stimulation-related side effects (Table 1). The "drivenness" in participant 1 was notable because it occurred on three separate occasions with increased left vBLA stimulation intensity, but not otherwise. Standard neuropsychological testing after 6, 24, and 48 months of stimulation revealed no deficits compared with pre-surgery baseline (Supplementary data. xls).

3.3. Neuroimaging

Preoperative MRI and postoperative CT scans were obtained, and electrodes were localized in the MNI space. Volume of tissue activated (VTA) was calculated based on the settings associated with long-term response (Horn et al., 2019) (Fig. 3 pdf). Participant-specific segmentation of the amygdala (Saygin et al., 2017) showed the electrodes centered in the basal nucleus, and the VTA involved the BLA complex. Normative tractography revealed that connections with the vmPFC (Brodmann areas 12, 11 and 25), anterior insula and hippocampus were associated with effective stimulation (Fig. 3 pdf).

The supplementary material contains rSUV FDG-PET values and raw data for amygdala, hippocampus, insula and vmPFC for both participants and healthy controls. Using the standard deviations for the controls as an estimate of those for the participant data we observed no significant effect of either provocation or surgery. For participant 2, the rSUV values for amygdala and hippocampus, but not insula or vmPFC, are approximately two standard deviations above those for controls and participant 1, possibly reflecting a persistent hypervigilant state for this participant or the heterogeneity of the population with PTSD.

4. Discussion

We found safety and some improvement in the long term for two veterans suffering from treatment-resistant PTSD who received bilateral basolateral amygdala DBS. Sustained improvement in refractory patients, particularly in the most severe and treatment-refractory

Table 1
Transient adverse effects of amygdala deep brain stimulation.[a]

	Month	Stimulation Change[b]	Symptoms	Time to peak onset	Time to off-set[c]
Patient 1	4.5–5	R vBLA 1.4 → 2.0 V AND L vBLA 0.7 → 1.1 V	Intolerable "Driven-ness;" need to move/go/engage	3–5 days	½-1 h
	6	R dBLA 1.4 V Added to R vBLA 1.4 V + L vBLA 0.7 V	Nausea	Same day. Initially tolerable but persisted, becoming intolerable over 2 weeks	5 min, complete in 1 h
	22	L vBLA 1.6 V → 2.0 V while R vBLA kept at 3.5 V	Intolerable "Driven-ness;" need to move/go/engage	5–7 days	1–2 h
	29	R vBLA kept at 3 V + L vBLA kept at 1.6 V while Frequency decreased from 160 → 100 Hz	Worsened sleep, intrusive symptoms and anxiety	5–7 days	2–3 days
	33	R vBLA kept at 3.5 V while L vBLA 1.6 → 2.0 V	Intolerable "Driven-ness;" need to move/go/engage	5–7 days	1–2 h
	60	Inadvertent stimulation at 120 us pulse width, 4.3 V R vBLA and 1.4 V L vBLA, 160 Hz.	Severe anger/nausea/negative hyperarousal	Immediate	<5 min when returned to 60 us pw, 4.3 V R vBLA, 1.4 V L vBLA, 160 Hz
	61.5	From to 4.3 V R vBLA bipolar 9-, 10 + and 1.4 V L vBLA 1-, case +.	Nausea, Visual and auditory Hallucinations; worsened insonia	1–2 weeks	Nausea in minutes; other symptoms in days
Patient 2	1	L vBLA 1.0 V, R vBLA 1.0 V; 90 uS and 160 Hz	Regular, extreme NM, severe anger and violent fantasies	Progressing over a month	Changed to L vBLA 1.5 V, R vBLA 1.0 V; 90 uS and 160 Hz No immediate effect
	2	L vBLA 1.5 V, R vBLA 1.0 V; 90 uS and 160 Hz	Worsened anger; outbursts with adverse consequences suicidal ideation without attempt	2 weeks	Changed to 1.5 V L vBLA +1.0 V R vBLA, 60 us, 160 Hz. Calmer in <1 h. Anger and motivation improved progressively over next 4 weeks with new functional engagement, volunteering at daughter's school.
	6	Both R and L BLA 1.2 V→1.4 V	Worsened subjective anger	2–4 days	<1 h
	9	From 1.4 V L, 1.4 V R vBLA, 60 uS, 160 Hz to 1.6 V L, 1.0 V R vBLA, 60 uS, 160 Hz	Intolerable motional Lability	2 days	< ½ hour
	34	From 1.6 V L vBLA; 1.4 V R vBLA 60 uS, 160 Hz to: 1.8 V L vBLA +1.4 V R vBLA 60 uS, 160 Hz	Worsened anger	1–2 weeks	<1 h

Legend.

d Except for 90 us in patient 2 during the first month (during double-blind conditions), stimulation was kept at 60 us pulse width for both subjects throughout the trial.

[a] Except at month 29 in patient 1, frequency was kept at 160 Hz.

[b] R and L vBLA and dBLA refer to right and left ventral and dorsal basolateral amygdala subregions, respectively; V refers to stimulation voltage.

[c] Time after return to previous stimulation settings before patient reported relief of unpleasant experiences.

symptoms observed–nightmares and dissociation in participant 1, and impulsive aggression in participant 2–is unusual for a placebo effect or the natural history of the syndrome. Furthermore, the unexpected worsening of symptoms, with battery depletion and recovery after battery replacement in participant 1 suggests a positive stimulation effect on symptoms. Findings from our brief sham-controlled stimulation periods provide some support for a direct effect of stimulation on clinical PTSD symptoms. Our connectivity findings (Fig. 3 pdf) are consistent with the hypothesis that BLA stimulation augments insufficient regulatory control from the vmPFC onto the BLA and correspond to the work of Hamani et al. (2022) who targeted the amygdala via the uncinate fasciculus with directional electrodes implanted in the subgenual cingulate gyrus. Our FDG-PET scans did not show provocation-related increase in amygdala or insula metabolism either before or after stimulation. Possibly a larger sample size could reveal this to be a type I error. Alternatively, a year after continuous stimulation, more complex rebalancing of activity in this brain circuit could have occurred resulting in failure to confirm our relatively simplistic hypothesis; this has been demonstrated in response to exposure therapy in combat PTSD, where complex amygdala, insula and vmPFC connectivity changes occur over time (Fonzo et al., 2021). Hamani et al. (2022) found increased left amygdala and right anterior cingulate FDG-PET metabolism 6–12 months after, compared with before DBS in 3 women participants.

Optimal clinical response appeared to correlate with increased stimulation intensity achieved over long-duration, similar to DBS in treatment-resistant depression (Crowell et al., 2019; van der Wal et al.,

2020; Alemany et al., 2023). These studies described balanced stimulation in terms of laterality, although variation in active contacts on each side. Our participant 2 similarly did best with bilateral stimulation, whereas participant 1 did best with R unilateral stimulation. Whether this is related to different symptom profiles in our two participants is speculative. Most functional neuroimaging studies have shown increased metabolic activity and BOLD signal for the right amygdala under provoked condition (Francati et al., 2007), but some showed left-sided predominance. Bijanki et al. (2020) described two individuals in whom unilateral right amygdalectomy for treatment-refractory epilepsy led to resolution of co-morbid TR-PTSD. However, Yrondi et al. (2020) showed onset of PTSD (from previously suppressed childhood trauma) after R temporal lobe epilepsy surgery. One seminal study we used in planning our investigation was that of Koenigs et al. (2008), who determined the lifetime prevalence of PTSD among veterans with penetrating brain injury in the Vietnam Veterans Head Injury databank. They found that none of the 15 soldiers who survived penetrating injuries with damage limited to the amygdala ever developed PTSD, whereas those with damage in other temporal regions but sparing the amygdala, or brain injury sparing the temporal lobes–except vmPFC, which was intermediate–had a lifetime PTSD prevalence similar to Vietnam combat veterans without brain injury. Among those 15 veterans, 7 had left, and 8, right-sided amygdala lesions. The laterality of amygdala activity leading to PTSD symptoms remains unclear and could differ based on original trauma. In this study, we sought to first demonstrate feasibility and safety of amygdala DBS. Consequently, we
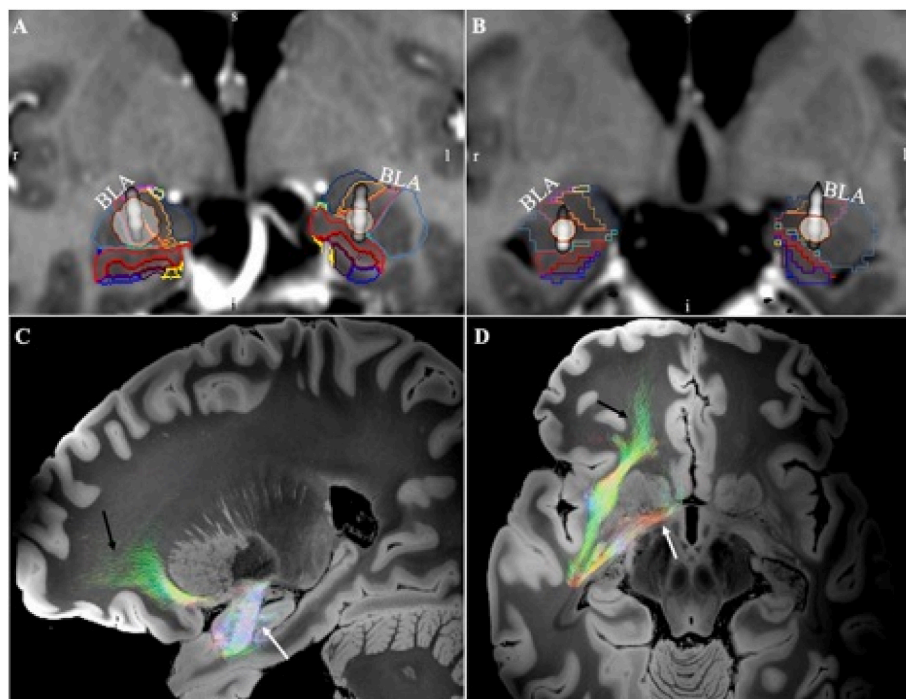
Fig. 3. Volume of Tissue Activated (VTA) Tractography

Fig. 3. Legend: A and B, Patient-specific amygdala segmentations in patient 1 (A) and 2 (B) showed that the VTA of the stimulation parameters at last follow-up (Patient 1: 1.4 v left and 4.3 v right; Patient 2: 3 mA; 160 hz, 60 *us*) involves mainly the basal segment and the most medial part of the lateral segment of the basolateral complex. L, left. R, right. S, superior. I, inferior. C, Normative tractography shows connections between the area stimulated in both patients with the hippocampus and the mPFC. D, The specific areas of the mPFC are connected with the amygdala through the uncinate fasciculus to Brodmann area 11/12 (black arrow) and through the ventral amygdalofugal pathway to the Brodmann area 25 (white arrow).

tested bilateral stimulation–which may be optimal for certain individuals—assuming this implies safety with unilateral stimulation. Future trials should consider systematic testing of laterality.

Resolution of dissociative symptoms was of great value for our participant 1. This effect was also observed in the initial case of SCG DBS of Hamani et al. (2020), and in one case of deep repetitive transcranial magnetic stimulation (rTMS; Blades et al., 2020).

DBS should be reserved for individuals with treatment-resistant illnesses like our participants. However, it is worth comparing DBS with less invasive neuromodulatory approaches. A number of studies have shown short-term benefit with varying parameters and treatment sites with rTMS (Petrosino, et al., 2021), and Hickson et al. (2024) recently found maintenance of response at 6-months in 57% of veterans. In the very recent trial of tDCS (as an augmentation to virtual reality exposure) in combat PTSD, van't Wout-Frank et al. (2024) found greater benefits in function, but non-significant difference in PTSD symptom change, with active treatment at 3-month follow-up. Other non-invasive neuromodulatory strategies have shown promise (reviewed in Koek et al., 2019; Becker and Milad 2023; Saccenti et al., 2024). However, none have the promise of DBS in-terms of maintenance of effects with external adjustability over years. Finally, in a previous publication (Lai et al., 2020), we found a limited 'sweet spot' of positive emotional valence with DBS at 2–3 V in a specific subnucleus in only one amygdala during Epilepsy Monitoring Unit testing–and this predicted optimal targeting with long-term stimulation. If replicable, this represents another advantage of DBS over extracranial stimulation.

We acknowledge limitations, particularly our small sample and mostly open-label data. Clinical changes could have been related to natural fluctuations in illness, co-morbidities, medications, psychotherapy or social factors. Importantly, we studied only two men with combat-related PTSD, and our findings may not generalize to women, persons of other genders; or to individuals with non-combat PTSD. Overall, our safety findings are encouraging, but given only two

subjects, deserve further investigation.

A limitation of open-loop DBS is the lack of direct feedback to monitor the effect of the stimulation. Both participants eventually underwent replacement of the pulse generator to the newer generation Medtronic Percept®, which allows monitoring of neural activity within a pre-specified frequency band. Participant 1 had achieved clinical remission by the time of Percept® implantation, so the monitoring capability was not used. The second subject received the newer system at Month 45 while still highly symptomatic. We used the automated spectrogram analysis of the device (BrainSense®, Medtronic) to select 6.9 Hz as the predominant frequency band. Targeting this allowed titration to higher stimulation intensities, with more sustained symptom reduction. Electrophysiological recordings in participant 2 showed sustained reduction in BLA theta power once stimulation reached 3 mA, a change that appeared to correlate with CAPS-IV reduction. This observation suggests a potential role for electrophysiology—in this case BLA theta–as a biomarker of target engagement in neuromodulation for psychiatric conditions where an immediate clinical effect is not always present. Further research is needed to replicate and extend this observation. We have initiated a study using closed-loop neuromodulation (Responsive Neurostimulation, NeuroPace™) of the amygdala to explore this approach (NCT04152993), with promising initial findings (Gill et al., 2023).

CRediT authorship contribution statement

Ralph J. Koek: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Josue Avecillas-Chasin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis. **Scott E. Krahl:** Writing – review & editing, Methodology, Investigation, Conceptualization. **James WY. Chen:** Writing – review & editing,

Methodology, Investigation, Formal analysis, Conceptualization. **David L. Sultzer:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Alexis D. Kulick:** Writing – review & editing, Investigation, Formal analysis. **Mark A. Mandelkern:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Maura Malpetti:** Writing – review & editing, Formal analysis. **Hailey L. Gordon:** Writing – review & editing, Investigation. **Holly N. Landry:** Writing – review & editing, Investigation. **Evan H. Einstein:** Writing – review & editing. **Jean-Philippe Langevin:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.05.008.

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