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Neuroplastic changes in patients with functional seizures following neurobehavioral therapy☆

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ABSTRACT

Given the high prevalence of functional neurological symptom disorder and its negative effects on the individual, family, and society, the development of interventions to treat it—including the subtype of functional seizures (FS)—is critical. Although we have limited understanding of the neurobiological effects of neurobehavioral therapy (NBT), studies indicate that NBT reduces seizures and improves psychological comorbidities in FS. In this study, healthy adults (N = 33) and patients with a history of TBI with (TBI-FS; N = 50) and without FS (TBI-only; N = 50) underwent magnetic resonance imaging (MRI) at 3 T approximately 12 weeks apart. TBI-FS participants underwent up to 12 sessions of NBT between scans. Structural MRI data were analyzed using voxel-based morphometry. A voxelwise repeated measures ANOVA tested changes in grey matter volume (GMV) between groups over time. Following treatment with NBT, TBI-FS participants showed a 1.23 % GMV increase in the left inferior and middle temporal gyri ($p_{FWE} < 0.05$) along with a 35.78 % reduction in seizure events and decrease in depressive ($p < 0.001$) and anxiety ($p = 0.01$) symptoms. Left temporal GMV increases were directly associated ($p = 0.04$, $r = 0.26$) with improvements in overall psychological, social, and occupational functioning ($p < 0.001$). We observed structural brain changes within the left inferior temporal gyrus following NBT that correspond to functional and psychological improvements in patients with TBI-FS. This work highlights the need for further research into the neurobiological effects of NBT, building on the relationship between NBT and brain plasticity and demonstrating putative targets for interventions.

1. Introduction

Functional seizures (FS), (also called psychogenic nonepileptic (PNES) or dissociative seizures), present with a complex array of physical, cognitive, and psychological symptoms along with various psychiatric features (Bakvis et al., 2009; Reuber and Brown, 2017; Reuber

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory-II; CAT12, Computational Anatomy Toolbox; FND, functional neurological disorder; FWE, family-wise error; GAF, Global Assessment of Functioning scale; GMV, grey matter volume; MRI, magnetic resonance imaging; NBT, neurobehavioral therapy; FS, functional seizures; QoL, quality of life; SPM12, Statistical Parametric Mapping; TBI, traumatic brain injury; VBM, voxel-based morphometry.

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and Elger, 2003; Reuber et al., 2011). The past two decades have witnessed a significant evolution in our understanding of FS and other subtypes of functional neurological disorder (FND), leading to improved recognition, diagnosis, and treatment across multiple medical specialties (LaFrance et al., 2010; LaFrance et al., 2014; LaFrance et al., 2020; LaFrance et al., 2009; Perez and LaFrance, 2016). This growing knowledge has spurred extensive research into the neurobiological underpinnings of these disorders. As a result, behavioral and neuroimaging studies of FS have revealed a spectrum of structural, functional, genetic, and neuroinflammatory abnormalities in brain regions crucial for inhibition, executive control, emotion regulation, and sensorimotor processing (Barzegaran et al., 2016; Van Der Kruijs et al., 2012; Balachandran et al., 2021; Szaflarski and LaFrance, 2018; Baslet et al., 2011; Perez et al. Inc; Sharma and Szaflarski, 2021; McSweeney et al., 2018; McSweeney et al., 2017; Asadi-Pooya, 2015; Asadi-Pooya et al., 2023; Labate et al., 2012; Allendorfer et al., 2019; Benbadis et al., 2022; Perez et al., 2021; Charney et al., 2024; Mueller et al., 2023a,b; Goodman et al., 2020).

Structural MRI studies have provided us with important insights on the neural correlates of FS, especially in patients with comorbid traumatic brain injury (TBI) (Labate et al., 2012; Sharma et al., 2021). Our previous study, which is the largest neuromorphometry investigation of TBI-FS to date, found that patients with TBI and subsequent FS exhibited significant atrophy in the right cerebellum and left inferior frontal gyrus, accompanied by reduced cortical folding and sulcal depth in parietal and insular regions (Sharma et al., 2021). Frontoparietal gray matter reductions correlated with more anxiety symptoms, while cerebellar alterations were linked to more depressive symptoms (Sharma et al., 2021). Aberrant folding patterns in brain regions involved in emotional processing and cognitive control, such as the insula, were predictive of overall symptom burden and functional impairment in daily life (Sharma et al., 2021). These findings have expanded our understanding of the neuroanatomical basis of FS and highlighted the importance of distinguishing between TBI-related vs. FS-related effects, particularly given the high comorbidity rate (approximately 50 % of patients with FS have a history of TBI) (LaFrance et al., 2013). One study clearly illustrates this relationship, reporting that 44.6 % of PNES patients had experienced TBI, with most cases (73.2 %, or 30 of 41 patients) classified as mild TBI (LaFrance et al., 2013). Furthermore, patients with TBI-FS exhibited significantly higher rates of mood disorders, impulsive behaviors, and disability compared to those with FS alone (LaFrance et al., 2013). Overall, the studies conducted to date have provided valuable information about the neuromorphometric changes associated with TBI-FS. However, further research is needed to determine the exact cause of these structural abnormalities and whether targeted therapies fulfill neurorestorative or neuroregenerative functions.

Neurobehavioral Therapy (NBT), a multi-modality psychotherapy, has been shown to reduce FS (Van Patten et al., 2024). A manualized, evidence-based, 12-session version of this treatment (initially described in earlier publications as Cognitive Behavioral Therapy (CBT)-informed psychotherapy (CBT-ip), and subsequently renamed NBT, returning to its original name (Reiter and Andrews, 2000), has shown a reduction in FS frequency, improvement in the severity of depression, anxiety, and somatic symptoms, and better quality of life (QoL) and psychosocial functioning (LaFrance et al., 2014). Adaptive coping, stress reduction, and emotional regulation were key elements of the original protocol, focusing on integrating mind–body techniques and addressing trauma-related aspects of FS (LaFrance et al., 2014; Espay et al., 2019). While a previous study revealed NBT-related white matter structural connectivity changes, NBT-related grey matter volume (GMV) changes have not been investigated to date (Mueller et al., 2023a,b).

The present study addressed an important knowledge gap by examining structural brain changes following NBT treatment in individuals with TBI-FS. Building upon our previous cross-sectional work, which represents the largest neuromorphometric study of TBI-FS conducted to date, we conducted a planned longitudinal investigation to track changes in GMV after therapeutic intervention (Sharma et al., 2021). We analyzed data from a subsample of TBI-FS patients from our parent study who underwent 12 weekly NBT sessions with pre- and post-NBT imaging, comparing their outcomes to healthy controls and TBI-only participants with repeated imaging. Healthy controls were specifically included to eliminate confounding effects from pre-morbid TBI. Based on previous research identifying brain regions typically involved in the development and maintenance of functional seizure symptoms, as well as cross-sectional analyses of our pre-NBT data, we developed hypotheses about NBT's neurobiological and clinical effects (Szaflarski and LaFrance, 2018; Sharma et al., 2021). Specifically, we hypothesized that patients with TBI-FS would demonstrate: 1) a significant post-NBT increases in GMV in frontal and temporal regions, 2) a substantial reduction in seizure frequency alongside improvements in depression and anxiety measures, and 3) a positive relationship between these structural brain changes and clinical improvements. The hypotheses guiding this trial and the planned analyses are detailed on clinicaltrials.gov (NCT03441867).

2. Methods

2.1. Recruitment

Sixty-two adults diagnosed with TBI-FS and 59 adults with TBI-only aged 22–63 years were recruited for a multisite neuroimaging study across three sites: 1) the Providence VA Healthcare System, 2) Rhode Island Hospital (RIH), and 3) the University of Alabama at Birmingham (UAB). A subset of these participants (50 TBI-FS, 55 TBI-only) were imaged twice and are included in the present study. Of the 55 TBI-only participants imaged twice, 5 participants' data were excluded from this analysis due to low image quality or the presence of substantial outliers and/or noise.

TBI-FS participants were scanned at pre- and post-12 sessions of NBT. TBI-only and healthy control participants were scanned twice, approximately 12 weeks apart. All protocols for study methods-exclusionary and inclusionary criteria and data collection procedures were uniform across the study sites and have been reported in detail previously (Mueller et al., 2023b; Goodman et al., 2020; Sharma et al., 2021). To further balance the dataset and more fully account for changes in GMV that may occur within this timeframe, healthy controls were also recruited using a separate protocol approved by both institutions' Institutional Review Boards (IRBs) (Allendorfer et al., 2025). We collected neuroimaging and basic demographic measures on healthy controls, but behavioral measures were not collected.

Participants with TBI-only and those with TBI-FS met the following inclusionary criteria: documented history of TBI; age range between 18 and 60 years; ability to undergo 3 T MRI; a negative pregnancy test on women of childbearing potential; and ability to complete questionnaires. Additional criteria for TBI-FS included video/electroencephalogram(EEG)-confirmed FS with at least one TBI preceding FS onset, and at least one non-epileptic seizure in the past year. Participants were additionally excluded if they were unable to complete self-assessments or had recent self-injury, suicidal intent, psychosis, disability litigation, or substance abuse. Participant's clinical history, medical records, and video EEG findings were reviewed to confirm TBI and FS diagnosis. FS were defined as paroxysmal, involuntary alterations in behavior, sensation, motor activity, and/or consciousness that resembled epileptic seizures but occurred without EEG epileptiform correlates (LaFrance et al., 2013). Patients with physiological non-epileptic events such as convulsive syncope or substance withdrawal seizures were excluded from the study. Definitive diagnosis of FS with video EEG was established using International League Against Epilepsy criteria (LaFrance et al., 2013). Co-morbid epilepsy was an exclusionary criteria, and no TBI-FS participants in the study had co-morbid epileptic seizures.

Participants provided written informed consent prior to study participation. All study procedures were approved by the VA, RIH and

UAB IRBs, and were carried out in accordance with the Declaration of Helsinki. All TBI-FS participants maintained stable medication throughout the study period (confirmed at each assessment).

2.2. Data collection and processing

Anxiety was measured with the Beck Anxiety Inventory (BAI), and depression was measured with the Beck Depression Inventory (BDI) (Beck et al., 1988; Beck et al., 1961). The Global Assessment of Functioning (GAF) scale measured the impact of each participant's symptoms on their everyday quality of life and psychological, social, and occupational functioning (Hall, 1995).

Imaging data were collected, processed, and analyzed as previously described (Sharma et al., 2021). High resolution T1-weighted structural images were collected on a Siemens Prisma 3 T scanner with a 64-channel head coil using a magnetization-prepared rapid acquisition with a gradient echo using the following parameters: repetition time = 2400 ms, echo time = 2.22 ms, field of view = 24.0 × 25.6 × 16.7 cm, matrix = 256 × 256 mm^2, flip angle = 8°, slice thickness = 0.8 mm, isotropic voxels. All neuroimaging data were collected at UAB and RIH using identical machinery, hardware, and software. Both facilities used identical scanner firmware, imaging sequence parameters, and scanning protocols. Scanning protocols were carefully matched across sites before commencing data collection, and each participant completed the pre- and post-NBT scans on the same machine at the same site. Biweekly quality assurance scan protocols were conducted using the Functional Biomedical Informatics Research Network (FBIRN) phantom at both sites to confirm the stability of signal-to-noise ratios, signal fluctuations, and signal drift between scanners (Keator et al., 2016).

Participants' T1-weighted structural images were pre-processed and analyzed using the Computational Anatomy Toolbox (CAT12) in Statistical Parametric Mapping (SPM12; https://www.fil.ion.ucl.ac.uk) running in MatLab R2020a (The MathWorks, Inc., Natick, MA, USA). Briefly, data were analyzed by voxel-based morphometry to estimate GMV in each voxel using the previously described data processing pipeline used for our baseline, cross-sectional analyses (Sharma et al., 2021; Ashburner and Friston, 2000; Ashburner, 2007; Ashburner and Friston, 2011; Tzourio-Mazoyer et al., 2002). Processing included skull-stripping, bias correction, tissue segmentation, spatial normalization to Montreal Neurological Institute (MNI) space, tissue modulation, and 8 mm full-width-half-maximum Gaussian smoothing (Keator et al., 2016; Ashburner and Friston, 2000; Ashburner, 2007; Ashburner and Friston, 2011). Total intracranial volume (TIV) was calculated during tissue segmentation and accounted for in statistical analyses by normalizing each individual's GMV values through proportional scaling.

2.3. Statistics

Descriptive statistics for all demographic and study measures were computed using GraphPad Prism version 8.0 (v.80) for Mac (GraphPad Software, La Jolla, CA, USA, https://www.graphpad.com). A Chi-square test of independence was performed to examine the distribution of biological sex across the TBI-FS, TBI-only, and healthy control groups; a one-ANOVA tested group differences in age. A series of repeated measures ANOVAs (rmANOVAs) compared changes over time in BAI, BDI, and GAF scores. Treatment-related changes in clinical measures were calculated as percent change ((post-NBT score minus pre-NBT score)/pre-NBT score × 100 %). For correlational analyses examining relationships between brain structural changes and clinical improvements, percent changes were used to normalize the data across different scales.

To assess GMV changes over time between TBI-FS, TBI-only, and healthy control groups, a voxel-wise rmANOVA computed group differences in GMV using permutation-based testing at 5000 iterations with the Multivariate Repeated Measures toolbox (MRM; https://github.com/martynmcfarquhar/MRM) running in MATLAB 2021a on a high-performance computing cluster (McFarquhar et al., 2016). Logarithmically scaled p-values were considered significant at $p < 0.05$, corrected for multiple comparisons using family-wise error (FWE).

For each rmANOVA, significant findings for the Group*Time interaction are reported, with a breakdown of the direction of the effect such that differences between TBI-FS and TBI-only or TBI-only and healthy controls are reported.

3. Results

3.1. Participant Demographics

Some of the imaging and behavioral measures data from this multifaceted study were previously published (Mueller et al., 2023b; Sharma et al., 2021; Van Patten et al., 2024; Allendorfer et al., 2024; Goodman et al., 2024; Goodman et al., 2023; Szaflarski et al., 2022; Byington et al., 2024). However, the pre-to-post NBT structural data or specific behavioral measures in this subsample of participants have not been presented to date. Here, we report findings for 50 participants with TBI-FS (37.7 ± 12.1 years, 33 females), 50 participants with TBI-only (38.0 ± 12.3 years, 23 females), and 33 healthy controls (35.0 ± 12.1 years, 17 females). Male to female ratios were stable across the TBI-FS, TBI-only, and healthy control groups (X^2 (4, $N = 133$) = 5.6, $p = 0.23$). Mean age was also similar across all three groups ($F(2, 130) = 0.70$, $p = 0.50$). For this reason, age and biological sex were not included in analyses as covariates of interest.

For the BDI, BAI, and GAF scores, a Group*Time interaction (Table 1, Fig. 1) showed that these scores significantly improved in TBI-FS participants from pre- to post-NBT, but not in the TBI-only group. BDI scores significantly decreased from 22.5 ± 11.9 to 13.3 ± 11.2 post-NBT for TBI-FS individuals ($p < 0.001$), whereas TBI-only participants' scores remained stable (13.4 ± 14.3 at Time 1, 12.9 ± 14.7 at Time 2). Similarly, BAI scores significantly decreased from 24.3 ± 10.8 to 17.4 ± 10.7 post-NBT for TBI-FS participants ($p = 0.01$), while TBI-only scores were consistent across timepoints (12.7 ± 13.1 at Time 1, 11.4 ± 10.8 at Time 2). Lastly, TBI-FS participants showed an improvement in GAF scores from 55.5 ± 7.9 at pre-NBT to 65.1 ± 7.8 post-NBT, contrasting with stable scores (77.9 ± 16.7 at Time 1, 78.7 ± 16.2 at Time 2) for TBI-only participants ($p < 0.001$).

The voxelwise rmANOVA revealed a significant Group*Time interaction ($p_{FWE} < 0.05$), which indicates that TBI-FS participants

Table 1
An overview of participants' scores on self-report assessments of anxiety, depression, quality of life, and global functioning.

	TBI-only (n = 50)		**TBI-FS (n = 50)**		
	Baseline	Post-SMC	Pre-NBT	Post-NBT	
Anxiety and depression					
BDI-II, total score	13.4 ± 14.3	12.9 ± 14.7	22.5 ± 11.9	13.3 ± 11.2	*
BAI, total score	12.7 ± 13.1	11.4 ± 10.8	24.3 ± 10.8	17.4 ± 10.7	*
Quality of life and functioning					
GAF, total score	77.9 ± 16.7	78.7 ± 16.2	55.5 ± 7.9	65.1 ± 7.8	*
SLC-90-R, GSI	0.8 ± 0.8	0.7 ± 0.7	1.1 ± 0.7	0.9 ± 0.7	
SLC-90-R, SOM	0.8 ± 0.7	0.8 ± 0.7	1.3 ± 0.8	1.2 ± 0.9	

The asterisk (*) denotes p-values that satisfy the statistical threshold ($p < 0.05$) for the Group*Time interaction.
Abbreviations: TBI, traumatic brain injury; FS, functional seizures; SMC, standard medical care; NBT, neuro-behavioral therapy; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; GAF, Global Assessment of Functioning (lower score indicates worse functioning); SLC-90-R, Symptom Checklist-90-Revised; GSI, Global Severity Index for the SLC-90-R; SOM, somatization subscale of the SLC-90-R.

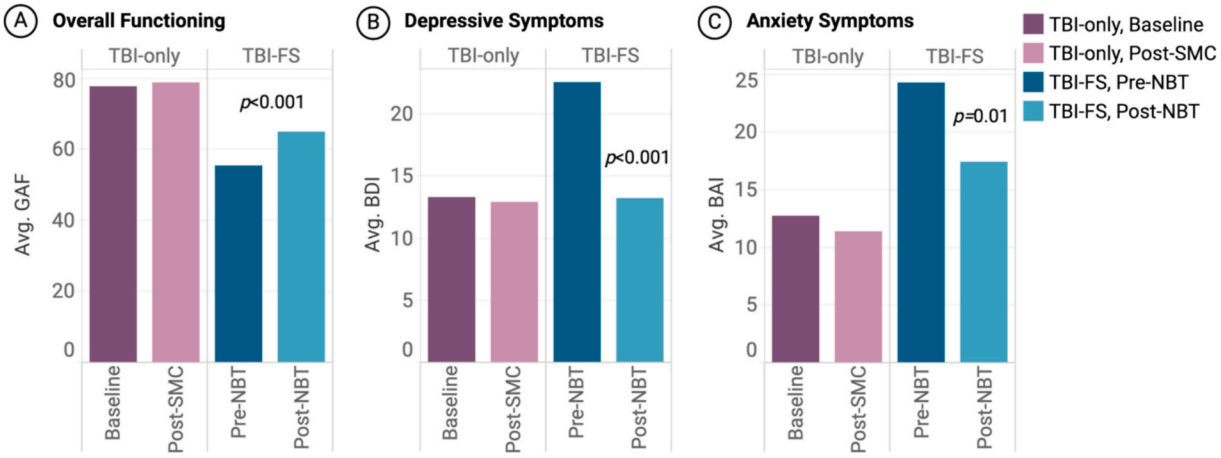

Fig. 1. Compared to patients with TBI-only, patients with TBI-FS demonstrated significant improvements in multiple measures: (**A**) improved overall psychological, social, and occupational functioning, as indicated by increases in GAF scores, along with significant reductions in depressive (**B**) and anxiety (**C**) symptoms, as shown by BDI and BAI scores, respectively… Abbreviations: TBI, traumatic brain injury; FS, functional seizures; NBT, neuro-behavioral therapy; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; GAF, Global Assessment of Functioning.

experienced an increase in GMV from pre- to post-NBT compared to both TBI-only and healthy controls (Fig. 2**A**). This increase was evident in the left inferior temporal gyrus (−63, −14, −26), expanding to sections of the middle temporal lobe (Fig. 2**A**). Additionally, TBI-FS participants had a 35.78 % reduction in FS events. Despite this substantial reduction, no significant relationships were identified between percent seizure reduction and % change in GMV and BDI or BAI scores. However, for TBI-FS patients, there was a significant positive association ($p = 0.04$, r = 0.26) between percentage (%) change in GAF scores and % change in GMV within the left inferior temporal lobe (Fig. 2**B**).

4. Discussion

4.1. Overview of neuroplastic changes following NBT

This study is the first to our knowledge to demonstrate structural changes in patients with FS following a psychotherapy intervention, specifically NBT. The objective of this study was to evaluate the neuro-morphometric correlates of NBT in patients with post-TBI FS using clinical and structural imaging measures. Consistent with previous NBT treatment studies, following NBT, TBI-FS participants demonstrated significant improvements in global functioning, reductions in depressive and anxiety symptoms, and fewer FS events (LaFrance et al., 2014;

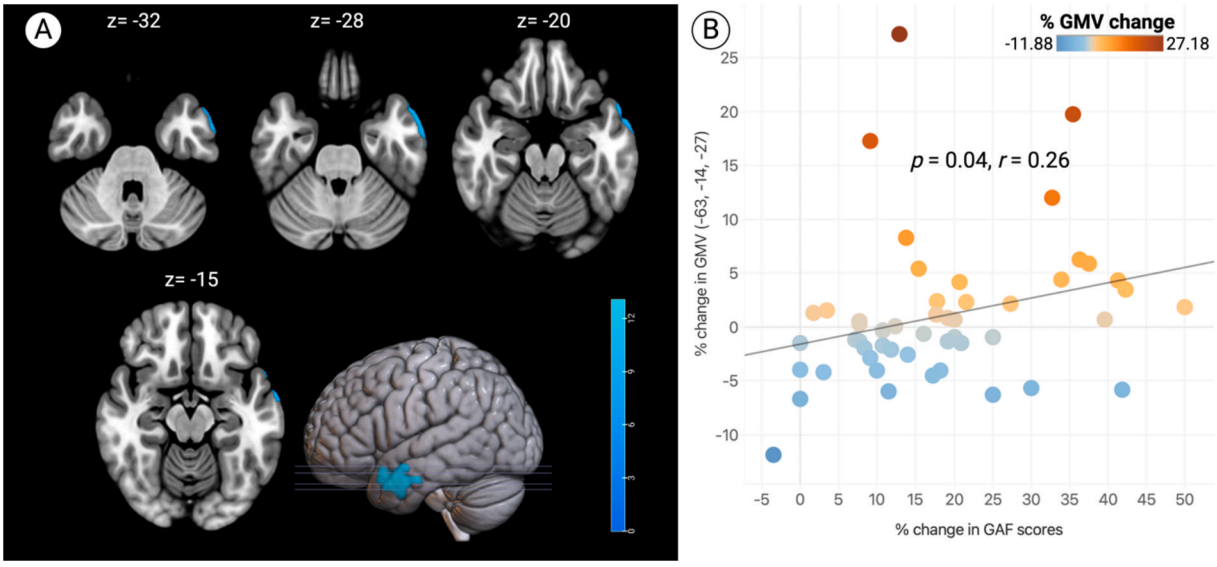

Fig. 2. Relationship between gray matter volume (GMV) change in the left inferior temporal lobe and functional outcomes in patients with TBI-FS, as measured by voxel-based morphometry and changes in global assessment of functioning (GAF) scores.. Anatomical rendering of significant GMV changes from pre- to post-NBT in patients with TBI-FS found within the left inferior temporal lobe. Cyan-colored regions indicate areas with statistically significant GMV changes, shown across four axial slices (z = –32, −28, −20, −15) as well as an anatomical 3D brain rendering for anatomical reference. The color bar represents t-values, with higher values indicating greater statistical significance.. Scatter plot illustrating the significant positive association between % change in GMV in the left inferior temporal lobe and % change in GAF scores. Each point represents data from an individual participant, with the orange to blue color gradient indicating the degree of change: light blue represents smaller GMV changes, while dark orange represents the largest GMV increases. A statistically significant positive correlation ($p = 0.04$, r = 0.26) demonstrates that greater GMV increases in GMV are associated with increases in GAF scores, suggesting a direct relationship between functional outcomes and structural changes in this region… Abbreviations: TBI, traumatic brain injury; FS, functional seizures; NBT, neuro-behavioral therapy; GAF, Global Assessment of Functioning..

Mueller et al., 2023b; Sharma et al., 2021). Most critically, we found significant GMV increases in the left inferior and middle temporal gyri after up to 12 weeks of NBT that correlated with improvements in global psychological, social, and occupational functioning as represented by GAF scores (Fig. 2). Overall, these results highlight the left temporal gyrus as a primary area where NBT in patients with TBI-FS may directly impact overall functioning and potentially improve quality of life, general mental health, interpersonal relations, and work-related performance. Furthermore, this study represents the first longitudinal neuroimaging investigation to specifically examine treatment-related GMV changes in TBI-FS and provides a potential roadmap for the development of interventions that promote neuroplasticity in FS, particularly in patients with premorbid TBI.

4.2. The role of temporal regions in language networks and cognitive control

Our analysis revealed that GMV increases post-NBT in TBI-FS patients were isolated to the left inferior and middle temporal gyri, which are regions critical for language processing, semantic memory, and sensory integration (Hickok, 2009). The observed GMV increase of 1.23 % in this region, particularly over a short time span, is remarkable when contrasted with the typical age-related GMV decline of ~ 0.24 % per year seen in the general population (Good et al., 2001). Interestingly, the regions where we found significant GMV increases were not the areas we previously identified as atrophic in TBI-FS patients, such as the right cerebellum and left inferior frontal gyrus (Sharma et al., 2021). We initially hypothesized that post-NBT GMV changes would occur primarily in these and other areas that form part of a network involved in FS generation and maintenance (Szaflarski and LaFrance, 2018; Sharma et al., 2021). Although our findings are different than initially hypothesized, the selective impact on the left inferior and middle temporal gyri warrants further investigation in order to understand why these regions are more likely to be affected by NBT than other structurally abnormal areas (Labate et al., 2012; Sharma et al., 2021; Ristić et al., 2015; Du et al., 2016; Steiger et al., 2017).

The left inferior and middle temporal gyri play crucial roles beyond their well-established functions in language processing and semantic memory. Recent studies in pediatric functional neurological disorder have identified these regions as key components of language networks that show abnormal connectivity patterns (Yuan et al., 2022). Specifically, the middle temporal gyrus has been implicated in frontoparietal networks that mediate cognitive control and executive functioning (Hickok, 2009; Yuan et al., 2022). The inferior and middle temporal gyri appear to function as critical nodes facilitating collaboration between frontal and posterior brain areas, supporting top-down regulatory processes such as the use of language-based strategies for emotional regulation (i.e., positive self-talk) (Hickok, 2009; Yuan et al., 2022). The post-NBT GMV increases observed in these regions may therefore represent enhancement of the neural infrastructure supporting improved cognitive control, executive function, and emotional self-regulation—processes that NBT directly targets. Since these temporal gyri are important constituents of the neural networks that support these processes, their structural enhancement may have cascading effects on broader neural systems involved in symptom management and functional improvement in patients with FS.

4.3. Comparing NBT to traditional CBT approaches

Understanding structural alterations in patients with neuropsychiatric disorders may provide a valuable perspective for interpreting the neuromorphometric changes observed in this study. Studies have shown that psychotherapy interventions such as CBT can significantly alter brain structure and connectivity in the short-term, impacting psychosocial function and mood in patients with psychiatric disorders, depression, and anxiety (Du et al., 2016; Steiger et al., 2017; Yuan et al., 2022; Enneking et al., 2020). For example, group CBT for mild depression has been shown to increase GMV in the right middle frontal gyrus and decrease GMV in the left postcentral gyrus (Du et al., 2016). In another study, Steiger and colleagues found that a 10-week course of CBT in patients with social anxiety disorder induced structural brain alterations that were linked with symptom reduction (Steiger et al., 2017). These changes included a post-CBT decrease in cortical volume in the left inferior parietal cortex, and increased fractional anisotropy in the bilateral uncinate fasciculus and right inferior longitudinal fasciculus (Steiger et al., 2017). Yuan and colleagues (2015) conducted a *meta*-analysis of findings from 13 studies and found that these investigations consistently reported post-CBT neural activity decreases within the left precuneus (Yuan et al., 2022). Cognitive tasks were associated with post-CBT activation decreases in the left anterior cingulate and left middle frontal gyrus, while emotion tasks were not associated with consistent patterns of changes (Yuan et al., 2022). Alterations in neural activity were predominantly confined to the default mode, executive control, and salience networks, suggesting that these regions may also mediate post-CBT changes in emotion regulation (Yuan et al., 2022).

In alignment with these findings, our study demonstrates that structural brain changes were observed following NBT in as little as 12 weeks. Our results show specific GMV increases in the left inferior and middle temporal gyri—regions that were neither hypothesized to change, nor implicated in CBT neuroimaging studies. This finding may be attributed to NBT's multimodality approach, extending beyond traditional CBT's "here and now" focus (LaFrance et al., 2014). While the protocol was initially characterized as a CBT-ip (for reader acceptance), the protocol is the same, with NBT utilizing multimodal therapeutic elements, including psychodynamic concepts, making the implicit explicit, linking the "here and now" with the "then and there," along with stress reduction, adaptive coping, and emotional regulation (LaFrance et al., 2014). In NBT, these components could selectively influence temporal regions associated with language processing, semantic memory, and multimodal sensory integration (LaFrance et al., 2009). NBT's emphasis on stress reduction may be a significant neuroplasticity-promoting feature, as down-regulation of the stress system has important effects on glucocorticoid production, epigenetic processes, and structural alterations in neural tissue (LaFrance et al., 2014; McEwen, 2017; Mourtzi et al., 2021). Thus, by modulating stress responses, NBT may create a neurobiological environment more conducive to adaptive neuroplasticity, particularly in regions that support cognitive and emotional regulatory functions (LaFrance et al., 2014; Davidson and McEwen, 2012).

4.4. Cellular mechanisms underlying observed GMV changes

It is important to note that observed GMV changes likely stem from cellular mechanisms, rather than a sheer increase in neuron numbers. One study demonstrated that changes in physical tissue volume cannot fully explain the GMV changes detected through VBM (Asan et al., 2021). These authors discovered that variations in nuclear volume and cell density contribute significantly to GMV increases, emphasizing the role of cellular modifications in structural changes identified by VBM (Asan et al., 2021). Beyond these mechanisms, neuroinflammatory processes may play an important role in the observed post-NBT GMV changes (Sharma and Szaflarski, 2021; Charney et al., 2024; Mueller et al., 2023a,b). Glial cells, the primary mediators of neuroinflammation, could undergo functional, morphological, and connectivity changes in response to therapeutic interventions like NBT (Campos et al., 2020; Cotter et al., 2001). Given that both TBI and FS have been associated with altered neuroinflammatory profiles, the post-NBT GMV increases observed in the present study could partly reflect normalization of glial cell function and morphology (Sharma and Szaflarski, 2021; Charney et al., 2024; Mueller et al., 2023a,b). Stress reduction components of NBT may particularly impact these processes, as chronic stress and elevated glucocorticoid levels are known to

influence glial cell function and neuroinflammatory signaling (Mourtzi et al., 2021; Tsuang et al., 2004; Kim et al., 2016). Therefore, these cellular-level changes could provide a mechanistic basis for the structural alterations found in the present study.

4.5. Clinical correlates of neuroplastic changes

The neurorestorative properties of NBT may be associated with the observed therapeutic benefit evidenced by the clinical improvements in TBI-FS participants. The GMV changes, however, did not correlate with changes in specific depression or anxiety measures, suggesting that the effect of NBT on seizures may be separate from its effect on mental health. Still, given the significant pre- to post-NBT improvements in clinical and imaging measures, as well as the significant relationship between changes in GAF scores and left temporal GMV, NBT may have indirectly stimulated cognitive processes, such as enhanced overall general functioning, coping strategies, and reduction in anxiety and depressive symptoms. While group analyses of VBM data may not highlight individual nuances, variations in neuroplastic responses to NBT could lead to region-specific alterations in post-NBT neuroimaging. Various factors such as environmental influences, inherent brain structure, genetic predisposition, and even individual variations in resilience could influence different brain regions that may respond uniquely to psychotherapies and interventions such as NBT (Tsuang et al., 2004; Goldwaser and Miller, 2020; Jiang et al., 2024; Fischer et al., 2018).

4.6. Neuroplasticity and Region-Specific Susceptibility to change

The post-NBT neuroplastic changes observed in the present study demonstrate the complex interplay between psychotherapy interventions and neurobiological processes that induce structural brain changes. Stress system modulation is a key target of NBT and may play a role in facilitating these changes (Allendorfer et al., 2019). First, stress system dysregulation has been implicated in FS generation and maintenance (Sharma and Szaflarski, 2021; Allendorfer et al., 2019; Mueller et al., 2023a). Chronic stress and elevated glucocorticoid levels impair neuroplasticity through differential effects on gene expression, cellular function, and connectivity in frontolimbic circuits (Perez et al. Inc; Price and Duman, 2020). By targeting stress reduction and adaptive coping, NBT may foster an environment that facilitates restorative neuroplastic processes by regulating gene expression related to neural plasticity and resilience (Davidson and McEwen, 2012; Goldwaser and Miller, 2020). These mechanisms likely include upregulation of brain-derived neurotrophic factor (BDNF) and transcription factors that coordinate plasticity-related gene expression (Tsuang et al., 2004; Goldwaser and Miller, 2020; Jiang et al., 2024; Fischer et al., 2018). Together, these epigenetic processes create a molecular bridge between psychotherapy interventions and MRI-detectable structural brain changes (Goldwaser and Miller, 2020). This epigenetically-mediated environment may support structural recovery in regions associated with emotional processing and cognitive control, as seen in the present study. Future research investigating these interconnected phenomena could reveal the specific mechanisms underlying NBT-induced neuroplasticity and potentially even identify biomarkers of treatment response, thus advancing the ongoing development of targeted interventions for patients FS and other subtypes of FND.

The potential for compensatory mechanisms and the dynamic nature of brain plasticity should also be factored into our interpretation of the longitudinal findings of this study. For example, concerning changes following NBT, the left inferior temporal gyrus may be more prone to neuroplasticity or more sensitive to environmental factors than areas that have been previously reported to be morphologically altered in children and adults with FS (Sharma et al., 2021; Kozlowska et al., 2017). Similar to the GMV increases observed after NBT in this study, others have demonstrated in adult stroke patients a significant increase in GMV in the somatosensory cortices after constraint-induced movement therapy (CIMT) (Gauthier et al., 2008). CIMT, similar to NBT, promotes neuroplasticity—the brain's ability to reorganize itself through the formation of new neuronal connections—after a brief but intensive treatment course (Gauthier et al., 2008). This may suggest that targeted therapies such as NBT may make certain brain regions, such as the left inferior temporal gyrus in this study, more susceptible to changes and thereby enhance their propensity to exhibit neuroplasticity.

4.7. Study Limitations and future Directions

Several limitations should be considered when interpreting the results of this study. First, the absence of a TBI + FS control group that did not receive NBT represents a methodological constraint. While the TBI-only group received treatment with SMC, the identified brain changes in the TBI + FS cohort attributable to NBT could be assessed in future studies by recruiting a TBI + FS group that does not receive the study intervention (however, since there is no longer equipoise between NBT and no treatment, an active control study would need to be designed) (LaFrance et al., 2014). The study significantly benefits from the collection of longitudinal neuroimaging data and the inclusion of both healthy and TBI control groups. This allows for investigating localized changes that are specific to TBI-FS following NBT and highlights the complex interplay between therapeutic interventions and brain plasticity in patients with TBI-FS. The substantial total sample size (N = 133 participants and 266 imaging studies), along with the robust sample size for each individual group, surpasses the criteria for a robust, well-powered neuroimaging study (Good et al., 2001). However, the smaller size of the healthy control group warrants caution in interpretation, since the effects of the larger TBI-only group might disproportionally influence the study's findings. Further research is needed to elucidate the mechanisms underlying the region-specific effects observed in the present study, particularly the pronounced effects in the left temporal lobe. Addressing this question is crucial for developing therapeutic strategies aimed at neurobehavioral pathways in diverse neurological populations. Most importantly, future studies should include multimodal imaging data. Studies of neurobiological and neurochemical response to treatment in conjunction with neuroimaging studies of interventions could also further disentangle the neurobiological underpinnings of FS/FNDs. Finally, further research is needed to clarify the processes driving the observed GMV changes in this study and to determine how increased GMV in the left temporal gyrus affects the broader neuromorphometric landscape and function in interconnected regions.

5. Conclusion

In conclusion, this study provides evidence that cortical structural brain changes were observed following NBT in patients with TBI-FS. The identification of GMV increases in the left inferior temporal gyrus underscores the need for further exploration of underlying mechanisms and highlights avenues for refining therapeutic approaches to support neuroplasticity and functional recovery in patients with FS and also those with a history of TBI.

Ethical Statement

The authors confirm that they have read the Journal's position on ethical publication, and this report is consistent with those guidelines.

Author Contributions

All authors listed made substantial, direct, and intellectual contributions to this work. Conceptualization: JPS and WCL. Data acquisition: JBA, AG. Data processing: AAS. Formal analysis: AAS. Data curation: WCL, JPS, AAS, and AG. Data visualization: AAS. Writing – original draft preparation: AAS. Writing – review and editing: AAS, JBA, SC, TG, AG,

LG, NP, WCL, and JPS. Study administration and review – JBA, SC, TG, AG, LG, and NP. Project supervision: WCL and JPS. Funding acquisition: WCL and JPS.

CRediT authorship contribution statement

Ayushe A. Sharma: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Jane B. Allendorfer:** Writing – review & editing, Software, Project administration, Investigation, Data curation. **Stephen Correia:** Writing – review & editing, Project administration. **Tyler E. Gaston:** Writing – review & editing, Project administration. **Adam Goodman:** Writing – review & editing, Software, Project administration, Investigation, Data curation. **Leslie E Grayson:** Writing – review & editing, Project administration. **Noah S. Philip:** Writing – review & editing, Project administration. **W. Curt LaFrance Jr.:** Writing – review & editing, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Jerzy P. Szaflarski:** Writing – review & editing, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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