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Research paper

# Restoring bottom-up communication in brain-heart interplay after trauma-focused psychotherapy in breast cancer patients with post-traumatic stress disorder

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ABSTRACT

*Background:* The psychological impact of breast cancer (BC) is substantial, with a significant number of patients (up to 32 %) experiencing post-traumatic stress disorder (PTSD). Exploring the emotional aspects of PTSD through the functional brain-heart interplay (BHI) offers valuable insights into the condition. BHI examines the functional interactions between cortical and sympathovagal dynamics. This study aims to investigate changes in functional directional BHI after trauma-focused (TF) psychotherapy, specifically Eye Movement Desensitization and Reprocessing (EMDR), in comparison to treatment as usual (TAU) among BC patients with PTSD. To our knowledge, this study represents the first examination of such changes.

*Methods:* We enrolled thirty BC patients who met the criteria for a PTSD diagnosis, with fourteen receiving EMDR and fifteen receiving TAU over a two- to three-month period. We analyzed changes in the emotional response during a script-driven imagery setting. Quantification of the functional interplay between EEG and sympathovagal dynamics was achieved using the synthetic data generation model (SDG) on electroencephalographic (EEG) and heartbeat series. Our focus was on the difference in the BHI index extracted at baseline and post-treatment.

*Results:* We found statistically significant higher coupling in the heart-to-brain direction in patients treated with EMDR compared to controls. This suggests that the flow of information from the autonomic nervous system to the central nervous system is restored following EMDR-induced recovery from PTSD. Furthermore, we observed a significant correlation between improvements in PTSD symptoms and an increase in functional BHI after EMDR treatment.

*Conclusions:* TF psychotherapy, particularly EMDR, appears to facilitate the restoration of the bottom-up flow of interoceptive information, which is dysfunctional in patients with PTSD. The application of BHI analysis to the study of PTSD not only aids in identifying biomarkers of the disorder but also enhances our understanding of the changes brought about by TF treatments.

## 1. Introduction

Breast cancer (BC) is one of the most common oncological diseases among women worldwide (Momenimovahed and Salehiniya, 2019). It entails significant psychological consequences, including anxiety, depression (Goerling et al., 2020) and traumatic stress (Cordova et al., 2017). Reports show that up to 32 % of women suffering from BC may experience post-traumatic stress disorder (PTSD) (Arnaboldi et al., 2017), with symptoms that include hyper-arousal, emotional numbness, intrusive thoughts, and flashbacks when asked to recall their diagnosis and cancer memories (Arnaboldi et al., 2014; O'Connor et al., 2011). This underscores the traumatic potential of a BC diagnosis as well as its

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possible impact on the course of the disease and the related treatments.

The literature on the neurobiological mechanisms of PTSD has grown rapidly over the last decade. At the level of the central nervous system (CNS), activity in the medial prefrontal cortex (mPFC) decreases, whereas it increases in the amygdala due to activation of the innate alarm system evoked by trauma-related stimuli or conditions (Lanius et al., 2020). Baek et al. (2019) highlighted the involvement of the superior colliculus (SC)-medio dorsal thalamus (MDT) pathway in mice. The SC is involved in visual-attentional processes and plays a crucial role in inner fear regulation (Evans et al., 2018; Wei et al., 2015). This structure targets the MDT, regulating emotional activity through a loop that involves the prefrontal cortex and the amygdala. The brainstem has also been suggested to play a crucial role (Felmingham et al., 2008) as has the midbrain periaqueductal grey (PAG) (Rabellino et al., 2017; Terpou et al., 2020) considering its functional connectivity to the default mode network (DMN), mediating high-order, self-related processing and innate and defensive responses (Lanius et al., 2020). These structures are involved in the central autonomic network (CAN), which integrates central (CNS), peripheral and autonomic (Autonomic Nervous System; ANS) functions and regions of the nervous system. The most studied index to investigate the ANS functions is heart rate variability (HRV). A pivotal meta-analysis (Chalmers et al., 2014) revealed reduced resting HRV in PTSD patients, and a recent study (Thome et al., 2017) revealed a lack of the CAN's regulatory capacity on ANS functioning at rest in people with PTSD, which could help explain some of the negative alterations in cognition and mood associated with this condition. Thome et al. (2017) also found that HRV values in the PTSD group were unrelated to functional connectivity within CAN-related brain regions, suggesting an uncoupling of the ANS from the CAN related to the failure of the top–down control of cardiac activity by higher-order brain regions. According to these authors, the lack of HRV-CAN covariation at rest may indicate that autonomic responses are not being regulated by the CAN in a top-down manner in PTSD. Furthermore, in the PTSD group, they found widespread resting state functional connectivity between CAN-related regions and other brain regions associated with emotional reactivity, motor readiness, self-referential processing, and sensory salience detection. The authors speculated that this may reflect the neurological correlates of a response pattern, indicating difficulty in differentiating between threat and safety situations and in developing context-appropriate responses. Given the widespread enhanced PAG resting functional connectivity seen in PTSD patients, it is even more likely that this pattern reflects a hypersensitive affective system at rest (Panksepp and Biven, 2012). In line with these findings, Rabellino et al. (2017) observed that the individual's ability to adaptively adjust parasympathetic outflow during exposure to stressful stimuli, either subliminal or supraliminal, via critical hubs of the CAN decreases with the severity of PTSD symptomatology.

A recent publication (Harricharan et al., 2021) proposed that traumatized individuals may have a limited capacity to perform multisensory integration, this contrasts with the experience of healthy individuals who are able to combine multiple sources of raw sensory information from their internal and external worlds to develop a unified coherent perception of a multimodal sensory experience. This limitation in trauma patients could be linked to an impairment in sensory processing, the ability to register, modulate and organize interoceptive and exteroceptive stimuli and, in turn, guiding adaptive and goal-oriented behavioural responses (Atick and Atickt, 2009; Baker et al., 2008; Chun et al., 2010; Gilbert and Sigman, 2007). An extremely stressful event in which one's health and integrity are perceived to be severely endangered can lead an individual's system to selectively focus attention on stimuli that are reminiscent of the traumatic event (Harricharan et al., 2021). In PTSD, this results in hypersensitivity to internal and external stimuli, increasing emotional and behavioural reactivity even to non-threatening stimuli. When the person's experience during the traumatic event is closer to the feeling of death and helplessness, the consequence may be a hyposensitivity, as in the dissociative subtype of PTSD.

To elicit and, thus, investigate emotional reactions in people with PTSD, the well-known "script-driven imagery" paradigm, which uses a participant's neutral and traumatic narratives (Orr et al., 1993), has been used to great effect. While the participants listen to their scripts, neurophysiological response data such as HRV (Bujarski et al., 2015) are recorded. The autonomic data obtained from the HRV index can be combined with neural response data provided by electroencephalography (EEG) to deepen our understanding of the role of functional brain-heart interplay (BHI) in the emotional processing of several psychiatric conditions (Catrambone et al., 2021a, 2021b, 2021c). Analysis of the coupling of brain and heart dynamics provides one potential route to revealing the complexities of the brain regions and functionalities involved in the autonomic control of the heart. In other words, the study of BHI offers a new perspective on the functioning of the CAN (Beissner et al., 2013; Benarroch, 1993; Valenza et al., 2016). Functional BHI analysis provides a more integrated description of two traditionally separate physiological systems in mediating both neurological and psychiatric disorders (Catrambone and Valenza, 2021). In addition to disclosing the underlying mechanisms of PTSD, neurobiological indices (such as BHI markers, or measures from EEG and HRV) can help optimise psychological treatments by emphasising the processes underlying the relationship between clinical improvement and neurobiological aspects.

Eye Movement Desensitization and Reprocessing (EMDR) therapy is a well-established psychological intervention used to address traumatic conditions and emotional dysregulation, including those experienced by cancer patients (Portigliatti Pomeri et al., 2021), and it is considered one of the elective treatment for PTSD (National Institute for Clinical Excellence, 2018; World Health Organization, 2013). Several studies have investigated the neurobiological correlates of EMDR showing morphometric changes in both limbic and cortical structures (Landin-Romero et al., 2018; Pagani et al., 2021; Trentini et al., 2021). Moreover, changes in brain activity have been shown after EMDR therapy, with an increase in brain activity in the frontal regions and a decrease in the limbic regions after treatment (Landin-Romero et al., 2018; Pagani et al., 2021; Trentini et al., 2021). Preliminary data showed that the high frequency (HF) components of HRV (i.e., parasympathetic activity) increased following EMDR sessions (Farina et al., 2015).

Previous research has evaluated the neurobiological impact of trauma-focused (TF) psychotherapy on people with PTSD. However, to date, no study has taken a perspective that integrates top-down processes, typically centred on the CNS, with bottom-up processes, which usually take into account the ANS. To fill this gap, the present study aimed to investigate the differences in functional BHI by comparing the effects of a TF psychotherapy - such as EMDR - with those of a treatment as usual - such as supportive therapy - (TAU) for the treatment of PTSD in BC patients.

## 2. Materials and methods

This study used data from a previous study (Carletto et al., 2019), which evaluated the effect of EMDR therapy compared to usual treatment (TAU) on PTSD symptoms in patients with BC and identified associated neurophysiological changes by only EEG. A full description of the study methods is provided in Carletto et al. (2019).

Women with BC and diagnosis of PTSD were recruited at the Breast Unit Service of the University Hospital "Città della Salute e della Scienza "in Torino (Italy) between September 2016 and November 2017. The study was approved by the local Research Ethics Committee. Informed written consent was obtained from all participants. Eligible patients underwent a three-step screening. Those who identified the illness as the traumatic event completed the Impact of Event Scale-Revised (IES-R; Weiss and Marmar, 1997) questionnaire. Patients with IES-R scores $\geq$33 received a PTSD diagnosis confirmation using the Structured Clinical Interview for DSM-5 (SCID-5; Weathers et al., 2018). The Clinician-

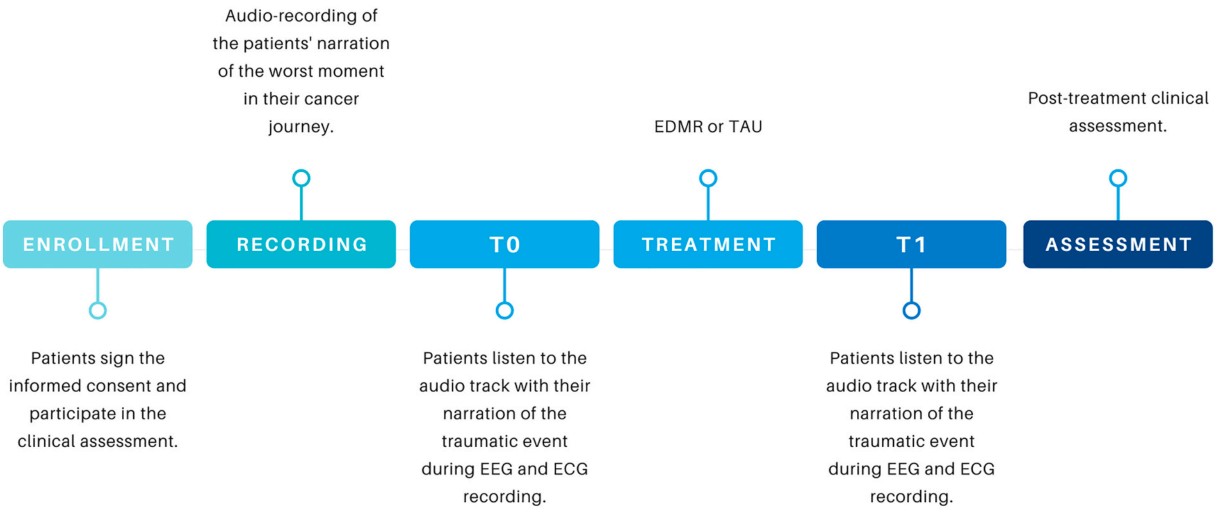

**Fig. 1.** EEG recording timeline at T0 and T1.

Administered PTSD Scale (CAPS-5; Weathers et al., 2018) assessed PTSD severity. A total of 30 BC patients met the criteria for PTSD diagnosis. Consecutive patients diagnosed with PTSD were asked whether they were willing to receive EMDR other than TAU. On reaching the maximum number of patients in the EMDR group, the remaining patients were assigned to the TAU group.

The TAU group received four supportive therapy sessions over two months, one session every other week. The therapy aimed to help patients cope with psychological symptoms related to BC. Two experienced psychotherapists provided the therapy and received supervision throughout the study.

The EMDR group received ten EMDR sessions over 2–3 months. EMDR followed Shapiro's protocol for traumatic events (Shapiro, 2001) and used a specific protocol for oncological patients (Faretta and Borsato, 2016). The first two sessions focused on stabilisation techniques, while the rest addressed trauma reprocessing. Three experienced practitioners provided EMDR with supervision from a certified senior EMDR supervisor.

The mean age was 55.47 (SD 7.64) in the EMDR group and 48.40 years (SD 9.42) in the TAU group. Except for a slightly higher age in the EMDR group, no significant demographic differences were observed between the two groups at the baseline. The pre- and post-treatment clinical results are presented in Carletto et al. (2019).

**Table 1**
BHI indices extracted through the model.

| Index | From | Band | To | Band |
|---|---|---|---|---|
| $C_{Brain_j \to Heart_{B_C}}$ | Brain | δ, θ, α, β | Heart | LF, HF |
| $C_{Heart_{B_C} \to Brain_j}$ | Heart | LF, HF, HT | Brain | δ, θ, α, β |

### 2.1. Estimation of functional BHI

EEG recordings were collected using a Galileo system (EBNeuro, Florence, Italy) while patients seated on a comfortable chair in a quiet room. Thirty-seven active electrodes were applied to the scalp using a pre-cabled electrode cap. Data were collected and digitised at a sampling rate of 1024 Hz. Participants were assessed by EEG at two separate time points: at baseline (T0) – all participants underwent two resting state EEG measurements, with eyes open and eyes closed before and after an EEG measurement during script-driven imagery; and post treatment (T1) – after the last session of EMDR or TAU treatment the EEG procedure was repeated. The EEG recordings were pre-processed using the so-called HAPPE pipeline, extensively explained in Gabard-Durnam et al. (2018). Fig. 1 shows the EEG recording timeline at T0 and T1. In brief, the pre-processing pipeline rejects as bad channels the 1 % tail electrodes external to the distribution built through the average log-power normalised joint probability and replaces them through a spherical interpolation algorithm applied to neighbouring channels. Frequencies below 1 Hz and the main electrical frequency noise at 50 Hz were filtered out exploiting a multitaper regression algorithm (Gabard-Durnam et al., 2018). Muscular and ocular artefacts and discontinuities were detected and rejected implementing a wavelet-enhanced independent component analysis (ICA)-based algorithm. A further fast-ICA algorithm was applied, and the extracted components were fed through a machine learning algorithm able to recognise artefact components (Gabard-Durnam et al., 2018). Finally, a common re-referencing procedure was employed (Candia-Rivera et al., 2021).

For the electrocardiographic (ECG) series, a MP160 research system by BIOPAC Systems was employed for the recording, using a 3-lead montage with a sampling frequency of 500 Hz. The well-known Pan-Tompkins algorithm (Pan and Tompkins, 1985) was used to detect R-peak events, and the series of time intervals between subsequent R-peaks were constructed and defined as RR-series. Possible physiological or algorithmic artefacts in the RR-series (such as ectopic beats or peak misdetections) were detected and corrected through the use of Kubios software (Tarvainen et al., 2014). A visual inspection assured the final quality of the retained recordings (i.e., EEG and RR series).

### 2.2. Spectral analysis

For the EEG, the power spectral density (PSD) was estimated using Welch's method, with a Hamming window of 2048 samples (2 s) with 1792 samples of overlap (1.75 s, 87.5 % of the Hamming window). The PSD was integrated in four classical EEG frequency bands: $\delta \in [1-4\,Hz)$, $\theta \in [4-8\,Hz), \alpha \in [8-12\,Hz), and\,\beta \in [12-30\,Hz)$.

For the HRV, the smoothed pseudo-Wigner-Ville distribution method (SPWVD) was employed (Orini et al., 2012). It estimates the PSD with a relatively low variance, and it has independent control of filtering in the temporal and frequency domains (Pola et al., 1996).

### 2.3. Quantification of functional BHI

The functional directional BHI was estimated using the synthetic data generation model (SDG) designed in Catrambone et al. (2019). In brief, the EEG series is modelled using a multiple-oscillator model (one for each considered frequency band), in which amplitudes of all oscillators are shaped using a first order exogenous autoregressive model.

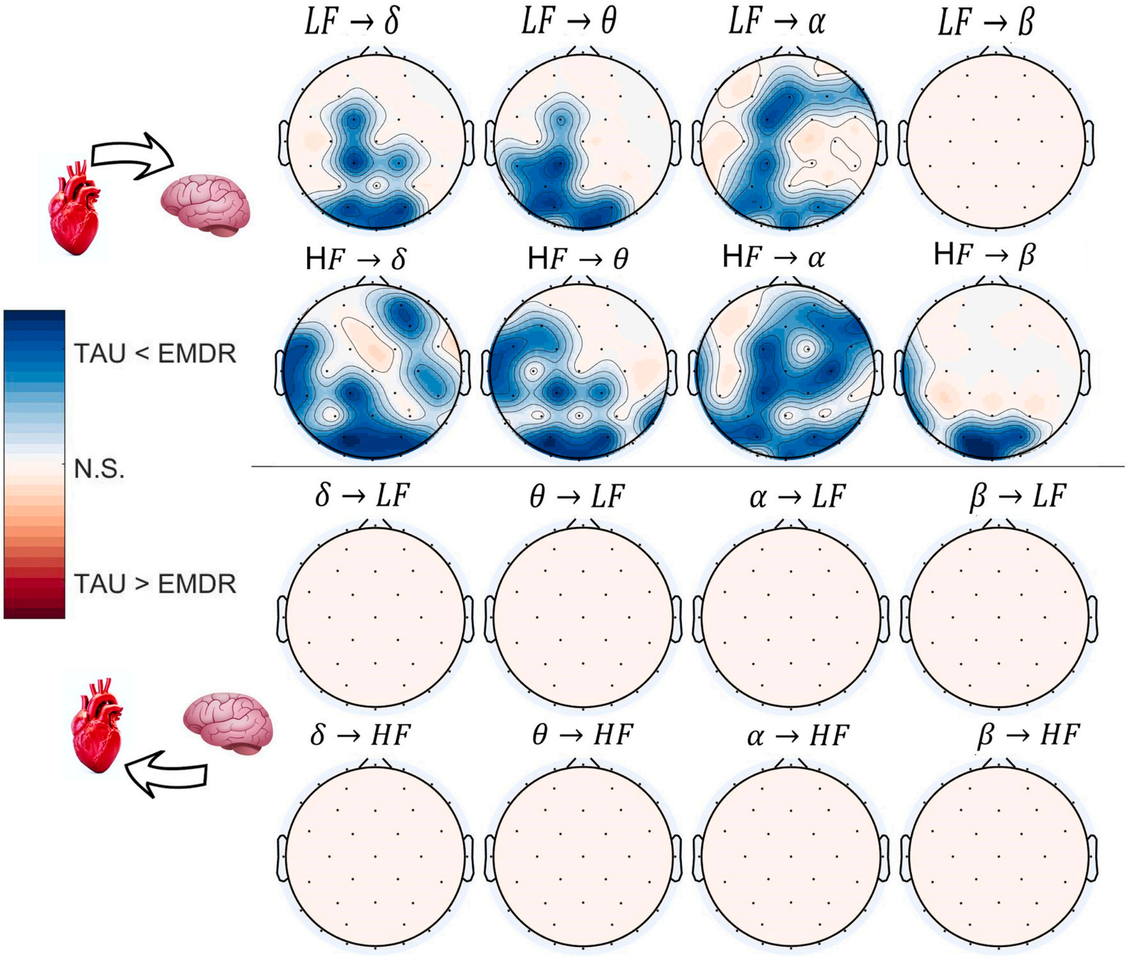

**Fig. 2.** *P*-value topographic maps from non-parametric Mann-Whitney tests for unpaired samples between $|BHI(T_0 - T_1)|$ during script experimental phases in TAU subjects versus those receiving EMDR. White areas indicate that changes between groups are not significant, whereas blue areas indicate that BHI changes in the EMDR group are significantly higher than those in the TAU group, and red areas indicate the opposite.
The statistical test compared the absolute difference between T0 and T1 during the script phase for the two experimental groups. Significant brain regions ($p < 0.05$, corrected through permutation test for multiple comparisons) are highlighted with respect to the green areas, which indicate no significant changes between conditions. Blue regions represent a BHI that is significantly higher in EMDR subjects with respect to the TAU group; reference regions represent the opposite. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The exogenous term accounts for the heart-to-brain interplay and it is specific for EEG and HRV frequency bands. It quantifies the strength of the coupling from a specific HRV frequency range to a specific EEG frequency range. Conversely, the model shapes the RR series with an integral pulse frequency modulation model, in which the autonomic activity accounts for low frequency (LF) and HF oscillations separately, the amplitudes of which are modelled to be influenced by brain activity through the brain-to-heart interplay term. This term quantifies the strength of the coupling from a specific EEG frequency band to a specific HRV frequency band. According to this model, both the electrophysiological dynamics (i.e., EEG and HRV series) are mutually dependent, and their interaction is modulated by the introduced coupling terms. In summary, a positive $C_{\delta\rightarrow LF}(t_k)$ indicates that the EEG-δ band, at time $t_k$, leads to a linearly proportional increase (i.e., it exerts a positive influence) in the HRV-LF band PSD time course. Employing the inverse model formulation, described in detail in Catrambone et al. (2021a, 2021b, 2021c, 2019), leads to the derivation of an entire family of BHI biomarkers. Through this framework, the directional BHI indices listed in Table 1 were derived. To implement the model, an easy-to-use MATLAB (Mathworks Inc., freely available online.[2]) implementation tool was exploited. In brief, the model quantifies the functional brain-to-heart directional interplay as well as the heart-to-brain directional interplay throughout the EEG oscillations in different frequency bands (i.e., δ, θ, α and β) and the HRV power in the LF and HF bands. Following recent evidence on autonomic dynamics, HRV-LF power was considered a marker of sympathovagal activity in this study, and the HF power a marker of vagal activity (Hopf et al., 1995; Pinna and Edwards, 2020; Reyes del Paso et al., 2013). To avoid confounding factors and to focus on the effect that the EMDR treatment might evoke, we considered the difference between BHI indices extracted during the first and second treatment (T0-T1) during the script-driven imagery sessions.

### 2.4. Statistical analyses

Intra-subject time-varying BHI estimates were condensed using the median value extracted in a specific experimental window (e.g., T0-

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[2] https://github.com/CatramboneVincenzo/Brain-Heart-Interaction-Indexes and https://it.mathworks.com/matlabcentral/fileexchange/72704-brain-heart-interaction-indexes?s_tid=srchtitle

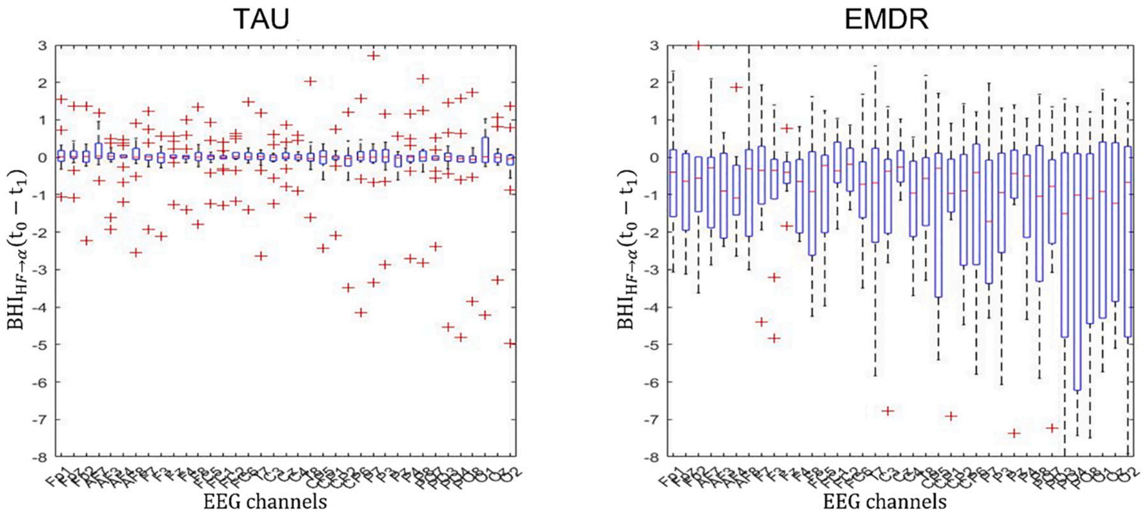

**Fig. 3.** Boxplots associated with the BHI index (HF → α) from the 37 EEG channels for the TAU group (left panel) and EMDR group (right panel).

script), and between-group statistical differences are shown as *p*-value topographic maps obtained from a non-parametric Mann-Whitney test for independent samples.

The group differences being statistically compared (i.e., EMDR vs TAU) involved functional BHI measurements in the following cases: i) script phase before treatment T0 ($BHI_{T0}$); ii) script phase after treatment T1 ($BHI_{T1}$); and iii) absolute difference between script phases at T1 and T0 (i.e., $|BHI_{T1} - BHI_{T0}|$). Moreover, Pearson's correlation coefficient analysis was performed to investigate whether functional BHI estimations were linearly correlated with the clinical parameters obtained through screening questionnaires (described in Carletto et al., 2019) before and after treatment (i.e., correlation between $|BHI_{HF\rightarrow\alpha}(T_0\ )|$ and $Q_{T0}|$ ). The statistical significance threshold was chosen to be $\alpha = 0.01$, and *p*-values were adjusted for multiple comparisons through permutation tests with 1000 permutations. A spatial cluster-mass permutation correction was applied to assess the physiological plausibility of the results (Friston et al., 1994): it assesses that when an electrode is found as significant it is enclosed in a larger group of significant electrodes, thus avoiding to consider spurious channels.

## 3. Results

No statistically significant differences were found between BHI estimations at time T0 (i.e.,$|BHI(T_0\ )|$) between the EMDR and TAU groups, in any scalp locations or frequency bands considered (Fig. S1 in Supplementary Material). At the post-treatment time point (T1), the EMDR group showed remission of PTSD in all treated patients, while no remission was observed in the TAU group (Fig. S2 in Supplementary Material).

The results show functional BHI changes in patients recovering from PTSD after EMDR therapy in the script phase after treatment ($BHI_{T1}$) with respect to the TAU group. To this end, the BHI SDG model (Catrambone et al., 2021a, 2021b, 2021c, 2019) was applied using the EEG and HRV series. The results from the statistical analysis of the SDG model output are depicted in Fig. 2. The white areas indicate that the differences between the groups are not significant, whereas the blue areas indicate that the BHI changes in the EMDR group are significantly higher than those in the TAU group. Red areas indicate that the BHI changes in the EMDR group are significantly lower than those in the TAU group. Fig. 2 reports the statistical analysis performed on the absolute value of the difference between the functional BHI indices extracted during the script-T0 phase and the BHI index extracted during the script-T1 phase (e.g., $|BHI_{HF\rightarrow\alpha}(T_0 - T_1)|$). Fig. 2 shows that almost all the combinations of heart-to-brain interactions (i.e., the first two rows) are diffusively significant, with the exception of the $BHI_{LF\rightarrow\beta}$ combination, whereas no significant differences were found in the opposite direction (i.e., brain-to-heart). More specifically, a central and dorso-parietal left region, together with a bilateral occipital one, are highlighted in the BHI indices from the sympathovagal LF band to the $\delta$ and $\theta$ EEG band, which is added a prefrontal right region in the $BHI_{LF\rightarrow\alpha}$ case. Considering the vagal HF band, a broader region, involving the posterior hemisphere and the temporal left lobe, is enhanced in the $BHI_{HF\rightarrow\delta,\theta,\alpha}$ statistics, with some peculiarity for each EEG band. In particular, a prefrontal right region is shown as statistically significant for the $\delta$ and $\alpha$ bands, and the latter also involves a broader central and parietal right region. A small significant group of electrodes is highlighted by the statistical analysis in the $BHI_{HF\rightarrow\beta}$ index, involving the occipital and left-temporal regions. It should also be noted that in all the aforementioned $BHI_{heart\rightarrow brain}$ significant analyses, the functional indices were higher in patients treated with EMDR than those receiving TAU.

To understand the differences between the EMDR and TAU groups better, in terms of absolute values of the differences in BHI indices

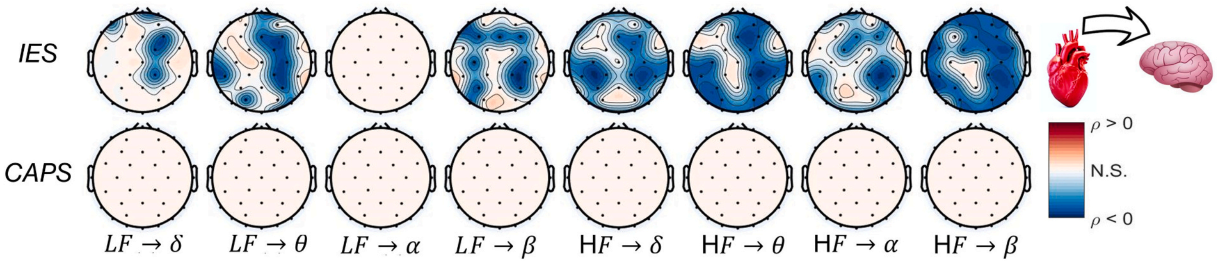

**Fig. 4.** Topographical representation of Pearson's correlation analysis of clinical parameters obtained using screening questionnaire results (i.e., IES-R and CAPS-5) and $BHI_{heart\rightarrow brain}$ indices at script-T1 phase in the EMDR group.

extracted before and after the treatment, Fig. 3 shows the boxplots associated with each of the 37 EEG electrodes. The TAU group shows values in a small interval, and close to zero, suggesting that the BHI indices extracted at T1 do not differ remarkably from those extracted at T0. Conversely, compared with the TAU group, the EMDR group has a more widespread distribution, with numeric values presenting a negative sign almost everywhere, thus suggesting that the BHI indices extracted at T1 are higher than those extracted at T0.

The results of the correlation analysis are shown in Fig. 4, and in the Supplementary Materials in Figs. S3, S4 and S5. To ensure statistical power robustness, we limited the correlation analysis to screening the questionnaires and BHI indices which resulted as being significantly affected by EMDR treatment. In particular, the IES-R (Weiss and Marmar, 1997) and the CAPS-5 clinical questionnaires and BHI indices in the heart-to-brain direction were explored. Fig. 4 depicts diffuse significant linear correlation in the EMDR-T1 phase, involving IES-R responses and all the EEG frequency bands and HRV bands (with the exception of the $BHI_{LF\rightarrow\alpha}$ indices). The highlighted scalp region spread from a centro-parietal right region for the $BHI_{LF\rightarrow\delta}$ to an almost ubiquitous significant correlation employing the $BHI_{HF\rightarrow\beta}$ indices. No significant correlation was detected for the CAPS-5 singular subscale scores. Notably, no significant correlation was detected in the T0 phase in either group; the associated results are reported in the Supplementary Material, in Figs. S3, S4 and S5.

## 4. Discussion

This study represents a pioneering attempt to evaluate the functional BHI in individuals with PTSD, along with the subsequent improvements observed following TF intervention when compared to TAU. Statistically significant higher coupling, in the heart-to-brain direction, was found in patients treated with TF psychotherapy (EMDR) compared with controls (TAU). Such a higher coupling occurred considering both the HRV-LF and -HF bands, at the heartbeat level, and different frequency bands at the central level, being the central axis between the hemispheres, from the midline frontal to occipital cortex, the most activated. Thus, it is plausible that the heart-to-brain interplay and communication empowerment is associated with the resolution of PTSD symptoms. This phenomenon, at this level, appeared to be quite generalised and not frequency specific.

The results of this study are consistent with the linear correlations observed in the clinical data of our previous study (Carletto et al., 2019), which show an improvement in PTSD symptoms accompanied by an increase in functional BHI after EMDR treatment. Comparing the two studies further, these findings are also coherent with the EEG results which highlighted the significant differences in delta and theta bands in the left angular and right fusiform gyri only in the group treated with EMDR, implying better communication between different brain regions (Carletto et al., 2019). Moreover, our findings appear to be in line with improved bottom-up and top-down regulation in response to successful treatment as highlighted in a systematic review on the neurobiological correlates of the psychotherapeutic treatment of PTSD (Malejko et al., 2017). Furthermore, our findings highlight the importance of bottom-up processes in TF psychotherapies.

Recent studies found that psychiatric, neurological and developmental disorders involving emotional dysregulation show altered interoceptive processing (Bonaz et al., 2021; Khalsa and Lapidus, 2016). The interoceptive system is a large collection of neural structures that cooperate to produce a real-time map of the body's homeostatic state (Carvalho and Damasio, 2021). Interoception entails signals moving from the non-neural interior of the organism to its neural central core – a bottom-up process – as well as broad reactions and control from the CNS to the periphery (Chen et al., 2021). This latter top-down component is assumed to incorporate cortically produced interoceptive predictions based on past experience (Carvalho and Damasio, 2021; Chen et al., 2021; Khalsa and Lapidus, 2016; Petzschner et al., 2021). According to Carvalho and Damasio (2021) “the interoceptive system monitors the state of the body and orchestrates automatic responses thereto”. The results of the present study show that interoception increases after EMDR, whereas interoception in the TAU group seems to be reduced, probably because of the activation of traumatic processes. In the TF psychotherapy group, the consequence is a decrease in the automatic and undifferentiated responses typical of PTSD, with an increase in the flow of bottom-up information and a recovery of the ability to discriminate the danger level of incoming stimuli.

Previously, Thome et al. (2017) described that, compared with healthy subjects, patients with PTSD show an uncoupling between ANS and CAN with a non-functional top-down regulation of autonomic responses. Thanks to the opportunity offered by the innovative BHI methodology, it is possible to assess CAN internal functioning. In their study of healthy subjects, Candia-Rivera et al. (2021) found that emotional processing is sustained by a bidirectional BHI. In particular, these authors hypothesise that emotional activation originates from the ascending flow of information starting in the ANS and integrates with the CNS (heart-to-brain), which triggers a cascade of neural activations that modulate central control over the periphery (brain-to-heart). Our results show that the flow of information in the direction from the ANS to the CNS appears to be restored following recovery from PTSD after TF psychotherapy (EMDR). It is possible to speculate that the reopening of the bottom-up communication flow (heart-to-brain) has cascading effects on emotional regulation mechanisms modulated by top-down processes (brain-to-heart), restoring the coupling between ANS and CAN found to be dysfunctional in PTSD patients in Thome et al. study (Thome et al., 2017), and thus associated with PTSD recovery.

The application of BHI could bring new life to studies on the neurobiology of psychological disorders as it offers a novel way of interpreting the data arising from existing assessment techniques (such as EEG, HRV, etc.), thereby providing additional information related to the communication flow (i.e., the exchange and integration of information) underlying emotional regulation (Candia-Rivera et al., 2022). BHI analysis offers the opportunity to delve into the mechanisms underlying psychological disorders by adopting a relational perspective between systems that will make it possible to identify markers linked to different mental disorders, which may favour earlier and more precise diagnoses in the future. BHI could facilitate the identification of treatment outcome markers, with the possibility of comparing different interventions, studying their effectiveness and investigating their mechanisms of action. Moreover, this methodology emphasises the important role of the ANS, supporting the idea of a visceral origin of the emotions (Candia-Rivera et al., 2022).

Due to its preliminary nature, this study has several limitations. First of all, the number of patients involved was low, and no control group, involving healthy subjects without PTSD, was employed. Another limitation is represented by the lack of a specific assessment of dissociative symptoms. Future studies should consider evaluating possible differences in the BHI between patients with PTSD and patients with the dissociative subtype (Nicholson et al., 2017) and include a follow-up investigation of the functional BHI to observe its correlation with how clinical changes are maintained or modified over time. Finally, the BHI methodology would also benefit from including an investigation of the role of the enteric system, which would expand our knowledge of the microbiota-gut-brain axis in different psychiatric disorders (Leclercq et al., 2016; Socała et al., 2021).

In conclusion, functional BHI analysis provides a novel approach to the study of PTSD, for identifying biomarkers of the disorder and for understanding the changes produced through TF psychotherapy. The results suggest that TF psychotherapy (EMDR) may favour a restoring of the bottom-up flow of interoceptive information that is dysfunctional in PTSD patients.

## Statement of ethics

The authors assert that the study was approved by the local Research Ethics Committee (University Hospital "Città della Salute e della Scienza" of Turin, Italy) and that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from participants to participate in the study.

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## CRediT authorship contribution statement

**F. Malandrone:** Investigation, Data curation, Writing – original draft. **V. Catrambone:** Formal analysis, Data curation, Writing – original draft. **S. Carletto:** Investigation, Writing – review & editing, Supervision. **P.G. Rossini:** Data curation. **M. Coletti Moja:** Investigation. **F. Oliva:** Validation. **M. Pagani:** Methodology, Resources, Project administration. **G. Valenza:** Conceptualization, Writing – review & editing, Supervision. **L. Ostacoli:** Conceptualization, Writing – review & editing, Supervision, Project administration.

## Declaration of competing interest

LO, SC and MP have been invited speakers at EMDR conferences. The other authors declare no potential conflicts of interest.

## Data availability statement

Data are available at https://github.com/CatramboneVincenzo/Brain-Heart-Interaction-Indexes and https://it.mathworks.com/matlabcentral/fileexchange/72704-brain-heart-interaction-indexes?s_tid=srchtitle.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.172.

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