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Intrusive experiences in posttraumatic stress disorder: Treatment response induces changes in the directed functional connectivity of the anterior insula

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ABSTRACT

Background: One of the core features of posttraumatic stress disorder (PTSD) is re-experiencing trauma. The anterior insula (AI) has been proposed to play a crucial role in these intrusive experiences. However, the dynamic function of the AI in re-experiencing trauma and its putative modulation by effective therapy need to be specified.

Methods: Thirty PTSD patients were enrolled and exposed to traumatic memory reactivation therapy. Resting-state functional magnetic resonance imaging (fMRI) scans were acquired before and after treatment. To explore AI-directed influences over the rest of the brain, we referred to a mixed model using pre-/posttreatment Granger causality analysis seeded on the AI as a within-subject factor and treatment response as a between-subject factor. To further identify correlates of re-experiencing trauma, we investigated how intrusive severity affected (i) causality maps and (ii) the spatial stability of other intrinsic brain networks.

Results: We observed changes in AI-directed functional connectivity patterns in PTSD patients. Many within- and between-network causal paths were found to be less influenced by the AI after effective therapy. Insular influences were found to be positively correlated with re-experiencing symptoms, while they were linked with a stronger *default mode network* (DMN) and more unstable *central executive network* (CEN) connectivity.

Conclusion: We showed that directed changes in AI signaling to the DMN and CEN at rest may underlie the degree of re-experiencing symptoms in PTSD. A positive response to treatment further induced changes in network-to-network anticorrelated patterns. Such findings may guide targeted neuromodulation strategies in PTSD patients not suitably improved by conventional treatment.

1. Introduction

Posttraumatic stress disorder (PTSD) is a disabling condition that can be triggered by terrifying events that have the potential to disrupt life, such as interpersonal violence, combat, life-threatening accidents or disasters, and global pandemics (Horesh and Brown, 2020). PTSD may lead to chronic psychiatric or addictive morbidities, loss of normal daily functioning, and increased risk of suicide (Lewis et al., 2019). This

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disorder usually induces intrusive symptoms (i.e., distressing recollections of the event, including flashbacks and nightmares, often called "re-experiencing symptoms"), persistent avoidance of stimuli associated with the trauma, negative alterations in cognitions or mood, and hyperarousal (American Psychiatric Association, 1994). ''Re-experiencing'' is considered central in the pathophysiology of PTSD, despite some similarities with other intrusive thoughts observed transdiagnostically, such as hallucinations, ruminations or persistent worries (Brewin et al., 2010; Laroi et al., 2012; Newman et al., 2013; Watkins, 2008). Although this research field is prolific, it still lacks a common neurofunctional signature for intrusive experiences that adequately circumscribes the underlying mechanisms of PTSD.

Brain-wide dysfunctions have already been suggested to be at the root of PTSD. The first functional magnetic resonance imaging (fMRI) evidence came from task-based studies, in which structures involved in memory and emotional processing (e.g., amygdala, hippocampus or ventral prefrontal cortex) were reported as key elements of the neurocircuitry of PTSD (Mahan and Ressler, 2012). Interestingly, another candidate node – the anterior insula (AI) - piqued the interest of trauma-focused scientists beyond fear-processing. Bilateral AI was indeed repeatedly found to be overactive in PTSD patients ranging from women exposed to intimate partner violence (Fonzo et al., 2010) to veterans (Duval et al., 2020). Crucially, the activation level in the insula (Stevens et al., 2018; Yehuda et al., 2015) was found to be associated with hyperarousal and re-experiencing, suggesting a specific role of the AI in these clinical dimensions.

On a more general level, AI appears to be one of the major connector hubs in the brain (van den Heuvel and Sporns, 2013). This structure has been implicated in a large variety of physiological functions, ranging from feeling representation to body and self-awareness (Gogolla, 2017). It receives convergent inputs from multiple sensory modalities, including the auditory and visual systems (Augustine, 1996; Bamiou et al., 2003; Butti and Hof, 2010; Mesulam and Mufson, 1982; Nieuwenhuys, 2012), while converging evidence supports AI's involvement in simultaneous attention to multisensory events (Bushara et al., 2003; Bushara et al., 2001). Thus, this brain area could have a particular involvement in intrusive experiences such as re-experiencing, characterized by important sensorial content, as has been previously shown in hallucinatory experiences (Jardri et al., 2013). The AI was also proposed to tag salient endogenous and external information and further reallocate attentional resources toward them (Menon and Uddin, 2010), making it a central element of the ''salience network'' (SN).

In addition to task-based fMRI studies, a second line of evidence about the role of AI came from correlational mapping between a seed and other regions of the brain, also called functional connectivity or FC approaches. These studies allowed us to explore how these areas cross-talk and potentially how they relate to clinical dimensions of PTSD. Similarly, the AI was found particularly involved. An increased FC was notably reported at rest between the bilateral insula with the lingual gyri and precuneus (both involved in implicit memory processing) in the dissociative subtype of PTSD (Harricharan et al., 2020). These resting-state dysconnectivity patterns were found to be state-dependent and susceptible to change when subjects with PTSD received adequate treatments.

For instance, following psychotherapy, the AI and amygdala exhibit increased reciproqual connectivity but also increased FC with the ventral prefrontal cortex and frontopolar and sensory cortices, while other regions, such as the left frontoparietal nodes of the central executive network (CEN), show decreased FC at rest (Fonzo et al., 2021). This is also the case for larger decreases in amygdalar–frontal connectivity and AI–parietal connectivity, both found to be associated with PTSD symptom reductions (Fonzo et al., 2021). These results suggest that subtle interactions between AI and the brain regions involved in cognitive control or emotional processing are associated with treatment response in PTSD.

Despite indisputable progress, we can ascertain that only a limited number of studies have explored in more detail the fine-grained influence that the AI exerts over other structures. A first study, conducted within the SN, evidenced a reduced dynamical causal flow from the right amygdala to the right insula (Weng et al., 2019), while pivotal changes in connectivity strength and temporal variability between the right AI and the middle frontal gyri were also measured (Rangaprakash et al., 2018), again supporting a key role for the AI in PTSD. In particular, specific explorations of the causal interactions between the AI and anterior cingulate cortex (ACC) revealed that the AI was able to amplify the detection of salience within the dorsal ACC (Cai et al., 2016; Chen et al., 2015), a finding that also appears compatible with electroencephalogram (EEG) spectral analyses showing that AI activation precedes that of the ACC (Chand and Dhamala, 2016), suggesting a possible causal role of the AI in these subtle SN interactions.

Strikingly, none of these studies assessed intrusive symptoms (and only one explored treatment response (Fonzo et al., 2021)) or the whole-brain directed functional or effective connectivity of the AI, since they limited the analysis to a predefined set of regions of interest. This approach may appear in contradiction with the well-accepted view that the brain is an interconnected network of functional components rather than composed of discrete units. The AI, and by extension the SN, appears to be one of these functional components.

We can illustrate this view by examining intrusive symptoms more broadly. SN effective connectivity was indeed proven to be involved in the process of switching from a state of unconstrained rest to one of experiencing hallucinatory events (Lefebvre et al., 2016; Palaniyappan and Liddle, 2012), reinforcing the hypothesis that this network may govern intrusive experiences in general. The SN is thus thought to tightly control the balance between various intrinsic networks and to swiftly move from rest to task-based actions and vice versa, a theory that has been conceptualized as the tripartite model (Koch et al., 2016; Lefebvre et al., 2016; Menon and Uddin, 2010; Sridharan et al., 2008; Stevens et al., 2018; Yehuda et al., 2015). According to this framework, the SN may drive commonly observed anticorrelated patterns between the default mode network (DMN, underlying self-referential processing) and the CEN (involved in cognitive control and decision making) (Menon and Uddin, 2010), an interaction already shown to be impaired in PTSD. Interestingly, surges in connectivity strength of the CEN were reported to be associated with intrusiveness (Koch et al., 2016; Nicholson et al., 2016; Sheynin et al., 2020; Weng et al., 2019).

Although encouraging, some gaps remain in our understanding of the exact network dynamics underlying intrusive experiences in PTSD and their resolution. We notably still lack causal proof about the directionality of the neural alterations underlying re-experiencing symptoms in PTSD. The present study intends to bring new insights to the dynamic role of the SN in PTSD and, more specifically, to circumscribe the directed influence of the AI over the rest of the brain as a function of treatment response. To do so, we analyzed fMRI data from a recent randomized controlled trial (RCT) comparing trauma memory reactivation therapy using propranolol (considered a putative reconsolidation blocker) versus the same therapy plus placebo in PTSD patients (Roullet et al., 2021). Similar designs have previously shown a significant symptom severity reduction after joint therapy (Brunet et al., 2018). Surprisingly, the most recent RCT did not confirm superiority for joint therapy with propranolol over therapy plus placebo (Roullet et al., 2021), but a significant proportion of patients nevertheless improved in both groups. We took this opportunity to explore dynamic brain markers of treatment response and decided to focus on re-experiencing symptoms, as one possible cause of limited treatment efficacy may rely not only on treatments themselves but also on the heterogeneity within PTSD or selective actions on certain clinical dimensions and not others (Neria, 2021).

Here, we hypothesize that effective therapy could modulate the directed functional connectivity of AI and that these plastic changes correlate with a reduction in trauma re-experiencing symptoms. In reference to the tripartite model, we also expect this downgrading in

intrusiveness to be linked to changes in DMN and CEN spatial stability, as previously shown in other models of intrusive experiences (Jardri et al., 2013), demonstrating a brain-wide reallocation of cognitive resources in PTSD patients who respond to treatment.

2. Materials and methods

2.1. Population

Patients with a primary diagnosis of PTSD according to the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria (Structured Clinical Interview for DSM-IV, PTSD module) and in the absence of contraindication to propranolol provided written consent to participate in the research (main characteristics and inclusion/exclusion criteria are reported in Table 1). No racial or genetic data were collected in this study. They all took part in an RCT testing for the efficacy of traumatic memory reactivation under the influence of propranolol versus placebo. This trial received approval from an ethics committee (CPP 2009-012976-29) and was registered on clinicaltrials.gov (NCT01713556). The main results for this clinical trial (i.e., that the efficacy of propranolol was not greater than that of placebo one week posttreatment) are presented elsewhere (Roullet et al., 2021).

Participants waiting for treatment were randomly and blindly allocated to two experimental groups (1:1 ratio): (i) a ''traumatic memory reactivation therapy + propranolol'' group and (ii) a ''traumatic memory reactivation therapy + placebo'' group. Propranolol or placebo was administered 90 min before the memory reactivation session, performed once a week for 6 consecutive weeks. The *Posttraumatic Stress Disorder Checklist Scale* - PCL-S (Ventureyra et al., 2002) was used to quantify symptom severity and assess treatment response. Because we were interested in re-experiencing symptoms, we focused on the item sum of PCL-S Q1-to-Q5 (Ventureyra et al., 2002). Assessments were made before treatment (at baseline) and one week after the end of the treatment (posttreatment). Patients had brief memory reactivation sessions with or without propranolol once a week for 6 consecutive weeks. The response to memory reactivation (with or without propranolol) in the whole sample (sometimes referred to as therapy in this paper for the sake of simplicity (Thierrée et al., 2020)) was considered positive for at least a 33% decrease (Brady et al., 2015; Mushtaq et al., 2012) in the PCL-S Q1-to-Q5 score compared to baseline. This threshold is commonly referred to as the first significant level of response, also called ''poor response''.

Table 1
Population description.

	Responders (n = 16)	Nonresponders (n = 14)
Age	41.3 (12.3)	36.6 (13.5)
Sex (Male /Female)	7/9	8/6
Education (%)*		
2	26.7	21.4
3	6.7	50
> 3	66.6	28.6
Dvars	24.3 (3.74)	24.1 (4.05)
Global signal	887 (121)	916 (96.3)
Total PCL-S score	65.4 (9.34)	68.4 (9.34)
PCLS-score (question 1 to 5)	18.9 (3.38)	19.4 (3.38)
Beck Depression inventory score	25.9 (14.5)	28.9 (11.3)
Rate of patients receiving propranolol *	*31.3 %*	*78.6%*

* $p < 0.05$. Level of education: International Standard Classification of Education 2011. Inclusion and exclusion criteria: primary diagnosis of PTSD according to DSM-IV-TR criteria (Structured Clinical Interview for DSM-IV, PTSD module), absence of contraindication to propranolol (hypotension, higher than a first-degree heart block, bronchial asthma etc.); medication recommended or suggested for PTSD treatment; psychotherapy; basal systolic blood pressure <100 mm Hg; basal heart rate <50 bpm; psychotic or bipolar disorders; traumatic brain injury; current substance or alcohol dependence; acute suicidal ideation; pregnancy and breast feeding.

2.2. MRI acquisition and data preprocessing

Patients underwent two MRI sessions at rest with their eyes closed (at baseline and posttreatment); a 3 T Philips Achieva scanner with an 8-channel head coil was used. Each of these sessions included a 4-min T1-weighted (T1w) 3D anatomical run (124 transverse slices, field of view = 256 mm^3, vox = 0.8 mm^3) and a 15-min T2*-weighted 3D principles of echo shifting with a train of observations (3D-PRESTO) sequence (Liu et al., 1993; Neggers et al., 2008; van Gelderen et al., 2012). This last sequence is a functional sequence (dynamic scan time = 1000 ms, TR = 22 ms, TE = 9.6 ms, flip angle = 9°, vox = 3.3 mm^3) allowing for full functional brain coverage with a temporal resolution particularly suited for effective or directed functional connectivity analysis (Deshpande and Hu, 2012).

Anatomical and functional MRI data were preprocessed using the FMRIPrep pipeline v. 1.5 (Esteban et al., 2019), a tool based on Neuroimaging in Python: Pipelines and Interfaces (Nipype v. 1.2.2) (Gorgolewski et al., 2011). T1w images were corrected for nonuniform intensity and skull stripped. Brain tissue segmentation of cerebrospinal fluid, white matter and gray matter was performed on the brain-extracted T1w image. Volume-based spatial normalization to the *Montreal Neurological Institute* ICBM-152 (MNI) template was performed through nonlinear registration using brain-extracted versions of both the T1w reference and the MNI template.

For functional images, a reference blood-oxygen-level-dependent (BOLD) volume and its skull-stripped version were generated and coregistered to the T1w image using a boundary-based registration algorithm with 9 degrees of freedom. Head-motion parameters were estimated before spatiotemporal filtering. Motion correction, BOLD-to-T1w transformation and T1w-to-template (MNI) warps were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) based on Lanczos interpolation. Spatial smoothing with a 6-mm isotropic Gaussian kernel was then performed, and a second "nonaggressive" denoising step was conducted using independent component analysis [independent component analysis-based automatic removal of motion artifacts, ICA-AROMA]. Linear trends were finally removed, and high-pass temporal filtering with 3 cycles/point was applied.

2.3. Granger causality analysis

Directed functional connectivity was assessed using Granger causality analysis (GCA), which allows for the data-driven exploration of a reference region's influence over the brain as well as targets of influence on the same given area (Roebroeck et al., 2005). We used this approach to account for the multiple regions naturally connected to the AI (Menon, 2015) and to avoid missing brain areas that could not have been retained in a more traditional theory-driven framework. Here, we used the implementation proposed in the BrainVoyager software suite (v21.4, BrainInnovation, Maastricht; *Granger Causality Mapping* plugin V1.5). We defined the bilateral AI, according to the *meta*-analysis from Laird (Laird et al., 2011), as the reference region for later analyses (right anterior insula (x = 35.76, y = 17.06, z = 9.71, number of voxels = 12008); left anterior insula (x = -35.53, y = 16.68, z = 6.88, number of voxels = 8787) – see Fig. 1). GCA maps were used to visualize the directed influences between the AI and every voxel in both directions after applying a gray matter mask. These maps were thresholded using a false discovery rate approach at q-levels of 0.01. We finally tested the association between GCA maps and symptom severity at the "post-treatment" time-point, considering $p_{fwe} < 0.05$ as significant. Finally, we used the generated instantaneous influence (i.e., correlations) as resting-state FC maps and followed the same analysis steps as previously described for GCA.

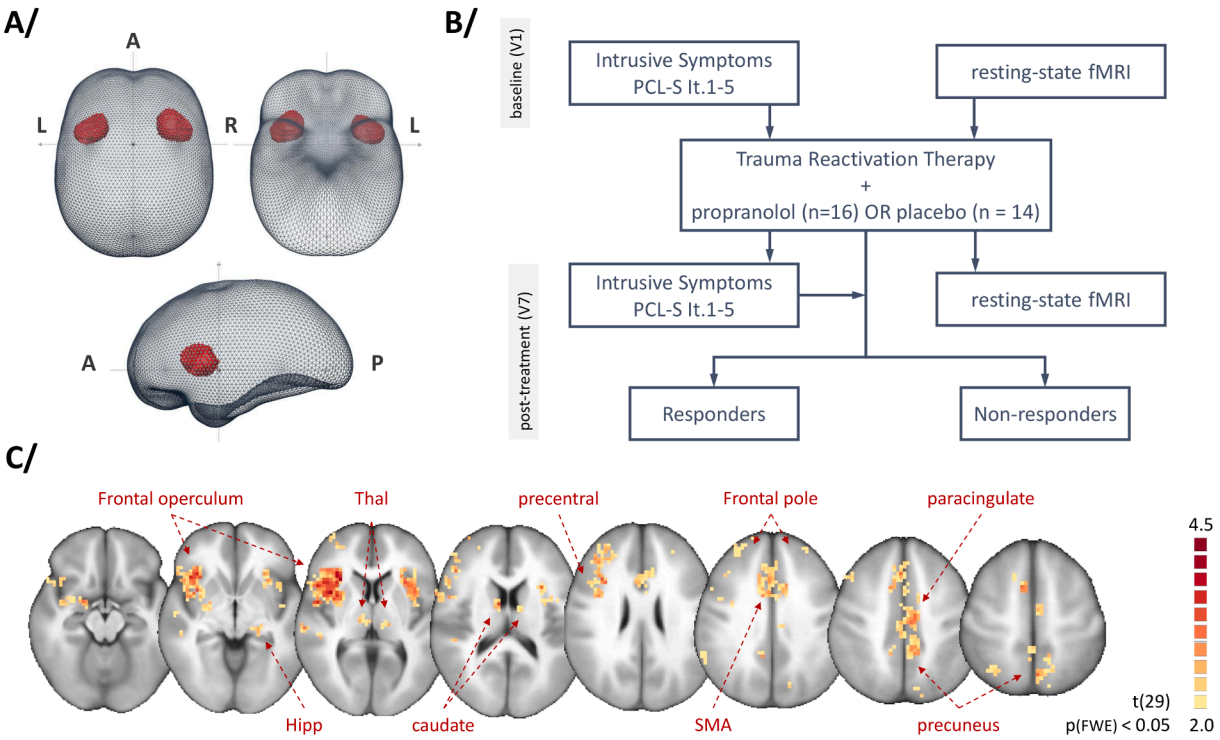

Fig. 1. Study design and *Granger causality analysis* (GCA) seeded on the anterior insula in PTSD patients. (A) The bilateral anterior insula was chosen as the region of interest for GCA and is presented in red in a glass brain. **(B)** Flow chart of the study. We defined responders as patients with at least a 33% decrease in PCL-S scores posttreatment compared with baseline. **(C)** Whole-sample random-effects GCA map at baseline. PCL-S: Posttraumatic Stress Disorder Checklist Scale; Thal: thalamus; Hipp: hippocampus; SMA: supplementary motor area; A: anterior; P: posterior; L/R: left/right sides of the brain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Main statistical analysis

To assess changes in AI functional and directed functional connectivity pre-/posttreatment between patients who responded to treatment (responders) and those who did not (nonresponders), we referred to a 2x2 mixed-model ANOVA using FC or GCA maps at baseline and post-treatment as within-subject factors and treatment response as a between-subject factor. Post hoc analyses used Student's t tests. All maps were then thresholded using a cluster-based permutation method (Forman et al., 1995). To prevent potential inflated false-positive rates (Eklund et al., 2016), we first specified a cluster-defining threshold (CDT) at $p_{uncorrected} < 0.001$. After conducting a 1000-iteration Monte Carlo simulation, a cluster-extent threshold was defined as a value high enough to keep the familywise error (FWE) at $p_{fwe} = 0.05$. The resulting brain areas were labeled using the Anatomy toolbox v 3.0 (https://github.com/inm7/jubrain-anatomy-toolbox (Eickhoff et al., 2005)).

2.5. Intrinsic network spatial stability measure

In parallel, we also explored the spatial stability of the DMN and the CEN posttreatment (i.e., the "posttreatment" time-point) using a "goodness-of-fit" (GoF) procedure. This method refers to the rate of spatial concordance between the resting-state networks and a given template (Jardri et al., 2013). After decomposing each posttreatment functional dataset using *independent component analysis* (ICA), we selected the components exhibiting the highest spatial correlation with an a priori template. For each participant, this procedure was repeated twice: with the DMN and the CEN template (Greicius et al., 2004). The resulting GoF scores were assumed to reflect posttreatment DMN and CEN spatial stability. We tested for an association between these GoF scores and the severity of re-experiencing symptoms using Pearson's *r* correlation test, considering $p < 0.05$ as significant.

3. Results

3.1. Demographic and clinical variables

Among the initial sample of 66 participants, 59 completed the treatment, and 30 performed the full pre-/post-fMRI assessment. At baseline, responders and nonresponders were comparable in terms of (i) sociodemographic characteristics (age and sex ratio) and (ii) symptom severity (PCL-S scores/subscores and depressive symptoms measured with the *Beck Depression Inventory* (Beck et al., 1988)). The distribution of the *Index Trauma* in the sample is reported in **Supp. Table 1**. Note that the responder group contained fewer patients receiving propranolol (Table 1, see (Roullet et al., 2021) for a more detailed description of the RCT main findings).

3.2. AI-directed functional connectivity before treatment

GCA performed on the whole sample at baseline revealed that the bilateral AI significantly modulates a group of regions involved in motor preparation, execution and action monitoring (i.e., precentral gyrus, the supplementary motor area, the left thalamus, and the frontal pole), as well as in visuospatial processing (i.e., the paracingulate gyrus and the precuneus). See Fig. 1 and **Suppl. Table 2**. No specific connectivity differences were evidenced between the responder and nonresponder groups before treatment.

3.3. Pre-/posttreatment AI resting-state and directed functional connectivity changes

Regions associated with significant [time-point × group] interaction in the resting-state seed-based FC analysis were the superior frontal, postcentral and angular gyri, the paracingulate gyri, the frontal and temporal pole, the precuneus, the parahippocampal gyri and the

cerebellum (Supp. Fig. 1).

The mixed-model ANOVA also revealed significant changes in AI causal maps after treatment. A significant [time-point × group] interaction was evidenced: (i) laterally, in the mid- and posterior insula, amygdala, precentral gyrus and supramarginal gyrus; and (ii) medially, in the cingulate cortex (anterior and posterior) and the precuneus. Compared with nonresponders, patients showing clinical improvement exhibited a reduced relative influence of the AI over a wide network composed of the superior frontal gyrus, anterior and posterior supramarginal gyri, anterior and posterior cingulate, central operculum and right amygdala. "Relative" needs to be understood here as a reduced influence of the AI on targeted networks, compared to the influence of the targeted networks over the insula. Conversely, nonresponders exhibited a lower relative influence of the AI over the precuneus (Cf. Fig. 2, Table 2). Simple pre-/posttreatment contrasts for responders and nonresponders are available in Suppl. Figs. 2, 3 and Suppl. Tables 3, 4, respectively. As a point of comparison, significant results for propranolol vs. placebo after treatment are presented in Suppl. Figure 4 and Suppl. Table 5.

To ensure robustness of the connectivity results, we conducted a series of complementary analyses listed below. First, since the anterior cingulate is the other core node of the SN (Menon and Uddin, 2010), we repeated the analysis using the ACC as a seed and found no [time-point × group] interaction. Second, because the right and left AI may subserve different functions, we also repeated the analyses using lateralized seeds for which overlaps with our main findings are reported in Supp. Fig. 5. Third, because some authors suggested that the traditional modeling of fMRI autocorrelation could be flawed (Cox et al., 2017), we repeated the analyses using an alternative approach that better controls FWE in cluster-thresholding methods. Agreements between the two methods are presented in Supp. Fig. 6.

3.4. Association with re-experincing symptoms severity

Regression analysis conducted posttreatment further revealed that the more severe the re-experiencing symptoms were, the greater the AI exerted a relative growing influence over somatosensory and motor regions (i.e., the posterior insula, right parietal operculum, and precentral gyrus), as well as over brain areas involved in visuospatial processing (the paracingulate gyrus) and self-other processing (i.e., the anterior and posterior cingulate cortices, superior frontal gyrus and supramarginal gyrus). See Fig. 3.

Table 2
Changes in the anterior insula directed functional connectivity between responder and nonresponder patients. Regions exhibiting a significant difference in *Granger causality analysis* maps between baseline and post-treatment according to treatment response. Coordinates are reported in the MNI (Montreal Neurological Institute) space.

x	y	z	t-value	p-value	Number of voxels	Label
−63	−45	36	−3.813837	0.000662	1073	Left Supramarginal Gyrus. posterior division
−57	−30	39	−4.072859	0.000328	770	Left Supramarginal Gyrus. anterior division
−6	−39	45	−3.452251	0.001728	368	Cingulate Gyrus. posterior division
−3	30	27	−2.993126	0.005594	369	Cingulate Gyrus. anterior division
6	−72	42	3.098338	0.004296	373	Right Precuneus Cortex
21	−9	66	−3.458369	0.0017	638	Superior Frontal Gyrus
27	3	−12	−2.894758	0.007138	341	Right amygdala
45	0	9	−2.875736	0.007479	798	Right Central Opercular Cortex

3.5. Intrinsic network spatial stability measure after treatment

Finally, the assessment of the spatial stability of the DMN and CEN posttreatment revealed that the severity of re-experiencing symptoms was positively correlated with the DMN GoF scores (**r = 0.521, p = 0.003**) and negatively correlated with the CEN GoF scores (**r = −0.418p = 0.021** - Cf. Fig. 3).

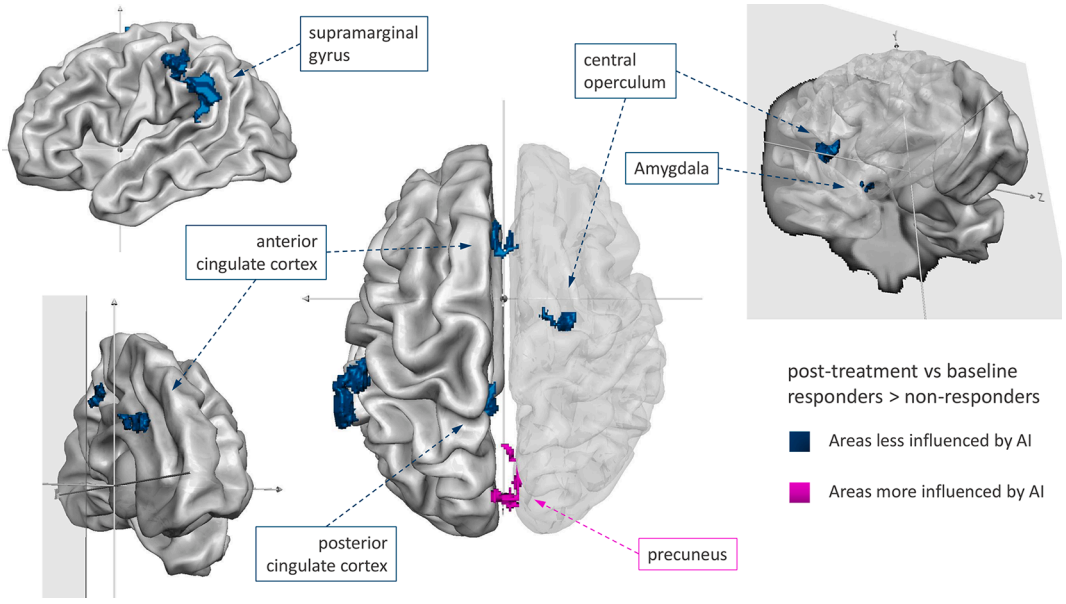

Fig. 2. Changes in *Granger causality* maps seeded on the anterior insula (AI) between responders and nonresponders to therapy in PTSD. We used a transparent right hemisphere to allow visualization of the deeper clusters. Brain areas less influenced by AI after effective treatment are depicted in dark blue. The precuneus (pink) was the only cluster found to be more influenced by AI posttreatment in responders than in nonresponders. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

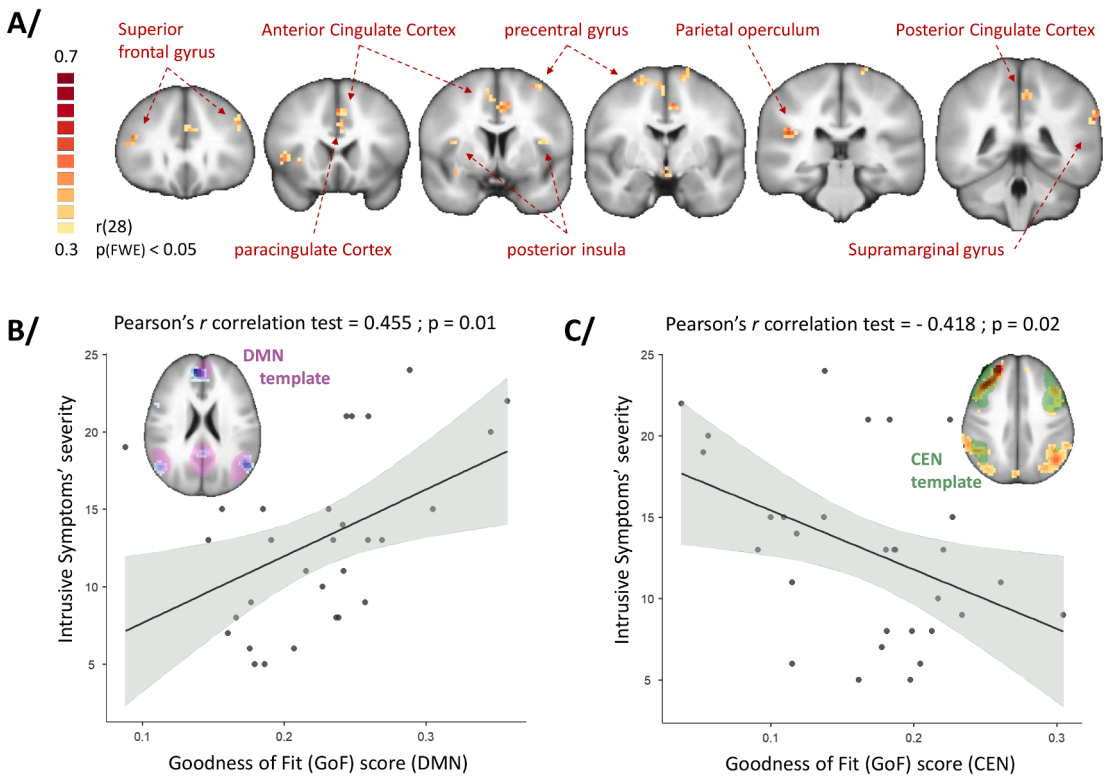

Fig. 3. Brain correlates of re-experiencing symptom severity in PTSD. (A) Linear regression analysis showing the brain regions exhibiting a positive association between the severity of re-experiencing symptoms and thresholded *Granger causality analysis* maps posttreatment. **(B, C)** Correlation analyses between intrinsic network stability and the severity of re-experiencing symptoms posttreatment. A positive association was indicated by default mode network stability (DMN GoF score), shown in **(B)**, whereas a negative association was indicated by central executive network stability (CEN GoF score), shown in **(C)**.

4. Discussion

The present fMRI study was designed to explore how an effective response to traumatic memory reactivation therapy (with or without propranolol) for re-experiencing symptoms in PTSD could modulate AI causal influences over the brain. Many fMRI studies measured pre-/posttreatment functional connectivity using correlations (Etkin et al., 2019; Korgaonkar et al., 2020; Santarnecchi et al., 2019; Zhu et al., 2018), but only a limited number of studies reported effective or directed functional connectivity changes in PTSD (Fonzo et al., 2021; Rangaprakash et al., 2018), with no particular focus on re-experiencing symptoms in a whole brain approach. Although AI is only one element of the SN, we focused on this region since it is known to be (i) a central integration hub serving sensory, emotional, motivational and cognitive functions and (ii) potentially involved in re-experiencing trauma. Even though the native RCT was not specifically designed to test for the prediction of response, we were able, using high temporal resolution fMRI and comparing pre-/posttherapy GCA results in PTSD patients, to provide new evidence that treatment response was associated with a significant relative reduction in AI-directed functional connectivity toward a wide motor, affective and self-other distinction, a global decrease that follows symptom severity reduction, allowing us to formulate hypotheses about a set of regions under AI influence that might mediate treatment response.

The first set of regions that seemed modulated by AI corresponded to limbic areas for which dense reciprocal connections with the ventral AI were repeatedly described. A strong body of evidence supports AI mediation in fear and anxiety, which was regularly found to be coactivated with the amygdala in stressful contexts (Gogolla, 2017). By showing a reduced relative influence of the AI on the amygdala in responders compared with nonresponders, we hypothesize that one of the first effects of treatment could be to temper the emotional storm associated with re-experiencing and hyperarousal (Yehuda et al., 2015). This finding nicely complements the existing literature in which joint amygdalar and insular overactivation is described in the context of PTSD (Koch et al., 2016) and declines after successful therapy (Malejko et al., 2017). The ability to better modulate AI connectivity following therapy may be associated with better cross-talk between untargeted inner thoughts and the ability to focus attention on stimulus-dependent demands (Szeszko and Yehuda, 2019), a theory also supported by the association found between symptom severity and AI influence over visuospatial areas. Using GCA, we were able to point out that the AI may primarily drive this pathological interaction in PTSD.

The second set of brain areas that seemed modulated by AI are involved in self-other distinction and may support dissociative experiences frequently observed in PTSD. This is the case for the precuneus, frontal superior and supramarginal gyri, all regularly found to be involved in self-awareness and agency processing (e.g., (Sperduti et al., 2011)). These cognitive functions are usually influenced by dorsal AI (Kurth et al., 2010). Interestingly, localized AI lesions can induce dissociative experiences, such as the (rare) "pain asymbolia" syndrome, in which pain recognition appears disconnected from its appropriate emotional response (9). Within this functional network, the supramarginal gyrus, located at the temporoparietal junction, has also been linked with experiences involving a sensorial component. Similar to the AI, the supramarginal gyrus receives heavy sensory inputs ranging from the auditory to the somatosensory modality. The crossmodal nature of this area makes it particularly well suited for linking sensory experiences with cognitive and/or affective information. Finally, the supramarginal gyrus is also involved in the phonological and articulatory processing of words (Stoeckel et al., 2009), making it solicitable by talking therapy. Again, this is perfectly in line with the present findings showing that the AI influence on this network was correlated with the degree of re-experiencing and was significantly decreased in responders.

The third set of regions that seemed influenced by AI is engaged in sensorimotor control (Chouinard and Paus, 2006; Dum and Strick, 1991; Paus, 2001) and might be involved in autonomic and behavioral responses to stress. Again, this interaction was found to correlate with symptom severity, even if only indirectly through the posterior insula and thalamic relays (Uddin et al., 2017), which were found to be under AI control at baseline. The motor network under consideration includes the caudal anterior cingulate cortex (cACC), the supplementary motor area and the precentral gyrus. Decreased resting-state functional connectivity between the caudal ACC (cACC) and the precentral gyrus was previously evidenced in veterans with or without PTSD compared to healthy controls, suggesting that military training or deployment, including trauma exposure, may influence SN connectivity (Kennis et al., 2014). In addition, precentral activity has been related to defensive behaviors in animals (Graziano and Cooke, 2006) and may subserve the increased "fight or flight" response regularly observed in PTSD when facing mental stress.

In addition to networks sustaining the rich phenomenology of PTSD symptoms, we also investigated how effective treatment may dynamically affect the interaction between intrinsic neural networks. We first demonstrated that the greater the AI exerted a causal influence over core nodes of the DMN (such as the rostral ACC, the posterior cingulate and the precuneus), the more severe re-experiencing symptoms were and that this interaction differentially changed according to the treatment response. This finding appears in line with previous studies conducted in schizophrenia patients (Lefebvre et al., 2016), showing that increased control from the SN to the DMN initiates hallucinatory states (another example of intrusive experiences). Interestingly, the DMN is also known to anti-correlate with task-related networks, such as the CEN (Fox et al., 2005; Greicius et al., 2003), and this antagonistic activity was proposed to be tuned by the AI (Sridharan et al., 2008). Returning to our schizophrenia example, a CEN takeover was found to drive the extinction of hallucinations (Lefebvre et al., 2016). Here, despite low GoF statistics, we found that re-experiencing trauma positively correlated with DMN stability and presented a reversed pattern for the CEN. These low GoF scores are close to those found in patients with schizophrenia (Jardri et al., 2013). One hypothesis that would need to be confirmed is that there may be a transdiagnostic decrease in the stability of resting networks. Altogether, these results support the idea that re-experiencing symptoms may correspond to self-referential mental activities driven by impaired AI control over the DMN/CEN balance, making salient memory fragments active enough (through bottom-up amplification) to aberrantly intrude into consciousness.

Despite these encouraging findings, some issues need to be further discussed. If the abovementioned theory is correct, we could expect to find the hippocampal complex among the regions relatively influenced by the AI. The limited sample size of the present trial may account for such a negative result, and the results with a small sample size need to be interpreted with caution when applying GCA to BOLD data (Seth et al., 2013). Especially, future studies can carefully look for hippocampal effects with larger sample size. Then, the exact relationship between the AI and this limbic structure will have to be clarified in future studies. In fact, several brain areas identified in this study have previously been shown to be involved in memory suppression beyond the medial temporal lobe. This is the case for the precuneus and the frontal cortex (Mary et al., 2020), which have tight connections with the hippocampus (Anderson et al., 2016; Cunningham et al., 2017). The same is true for other limbic structures, such as the amygdala, which have strong reciprocal connections with the hippocampus. We cannot exclude that intermediate small brain structures, such as the hippocampus, that are involved in a chain of causality could be more vulnerable and may not survive statistical thresholding. Based on this possibility, we hypothesize a triple interaction [AI - amygdala - hippocampus] at the root of the memorization of trauma-related emotional valence, constituting an interesting complementary track for future research on PTSD.

A second potential issue resides in the fact that GCA indicates the dominant direction of influence, introducing ambiguity in the interpretation of pre-/posttreatment contrast maps, as they may potentially result from a decrease in the influence of AI-to-target-region influence or from an increase in the influence of target-to-AI. For the sake of simplicity, we referred to the influence of the AI on other regions in the manuscript. However, this problem can, for instance, be illustrated by considering a recent study of effective connectivity in PTSD that reached seemingly opposite conclusions, suggesting that frontal regions exerted a reduced influence on AI (Rangaprakash et al., 2018). In the same vein, a decreased causal flow from the right amygdala to the right insula in PTSD patients relative to trauma-exposed controls has been suggested (Weng et al., 2019), which again appears in apparent contradiction with the present findings. Even if the samples and designs were not exactly comparable, methodological advances should help to reconcile these findings, but until then, this literature needs to be interpreted with caution and in reference to clinically and anatomo-functionally available knowledge at the time of publication.

A third potential issue could be in the use of AI seeds instead of the whole SN. We know that large volumes of interest (VOIs) average many voxels, risking a loss of temporal detail. More importantly, although a large cluster of voxels may have been activated in the same contrast, some of those voxels may be differently functionally (or effectively) connected to other parts of the brain. We considered that computing GCA maps for VOIs averaged over functionally different regions would yield maps that show a mixed average of the involved functional networks.

A final point we would like to insist on is that we focused on symptom reduction, regardless of the initial group of randomization in the *Pre-Reactivation Propranolol Therapy* trial. Of course, the full results of the RCT have been presented elsewhere (Roullet et al., 2021) and are beyond the scope of the present paper. Note that the between-group differences in our study were explained by changes in both the responder and nonresponder groups. This is compatible with previous studies showing that psychotherapy could induce functional changes, even in cases of nonsignificant clinical response (Simmons et al., 2013), that could be linked with repeated trauma exposure without extinction, as suggested in previous studies (Uddin et al., 2017). Importantly, because half of the sample did not reach the threshold for a positive response to therapy, we expect our findings to also be relevant for future neuromodulation trials for severely impaired PTSD patients. Neuromodulation methods such as transcranial magnetic stimulation usually target superficial cortical areas, and the AI could constitute a better target for neurofeedback methods that allow modulation of the activity/connectivity of profound or subcortical structures. Promisingly, a recent study confirmed that PTSD patients could be trained to downregulate amygdalar activity using real-time fMRI-based neurofeedback (de Pierrefeu et al., 2018).

Overall, we were able to provide experimental support for a role of AI connectivity in treatment response. Notably, we showed that effective therapy was linked with plastic changes in AI-directed influence over sensorimotor, cognitive and emotional networks. Dynamically, restoration of the DMN-to-CEN switch control was also observed, offering an attractive mechanism for re-experiencing. We hope that the present results will contribute to paving the way for new evidence-based treatments of intrusive symptoms in PTSD, considering the AI as a particularly interesting target for this purpose.

CRediT authorship contribution statement

Arnaud Leroy: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Etienne Very:** Conceptualization, Writing – original draft, Writing – review & editing. **Philippe Birmes:** Conceptualization, Writing – original draft, Writing – review & editing. **Pierre Yger:** Formal analysis, Writing – review & editing. **Sébastien Szaffarczyk:** Conceptualization, Formal analysis, Writing – review & editing. **Renaud Lopes:** Conceptualization, Formal analysis, Writing –

review & editing. **Olivier Outteryck:** . **Cécile Faure:**Conceptualization, Writing – review & editing. **Stéphane Duhem:** Conceptualization, Writing – review & editing. **Pierre Grandgenèvre:** Conceptualization, Writing – review & editing. **Frédérique Warembourg:** Conceptualization, Writing – review & editing. **Guillaume Vaiva:** Conceptualization, Writing – original draft. **Renaud Jardri:** Conceptualization, Formal analysis, Writing – original draft.

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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Disclosure

AL is consultant for Kinnov Therapeutics. RJ has been invited to scientific meetings, and boards with compensation, by Lundbeck, Janssen and Otsuka. None of these links of interest are related to the present work. All the other authors have no conflict of interest to declare.

Author contributions

AL, EV, PB, SS, RL, CF, SD, PG, FW, GV, RJ contributed to the conceptualization of the work.

AL, PY, SS, RL, RJ contributed to the formal analysis.

AL, EV, PB, GV, RJ contributed to the Writing-original draf of the work.

AL, EV, PB, PY, SS, RL, CF, SD, PG, FW, GV, RJ contributed to the Writing - review and editing of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.102964.

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