Changes in brain activity associated with cognitive-behavioral exposure therapy for specific phobias: searching for underlying mechanisms

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Introduction. The current evidence collected consistent results about morphological and functional brain changes produced by psychological treatment. Exposure cognitive-behavioral therapy (CBT) is currently the most effective psychological treatment for phobias.

Aims. To explore the brain activation and self-reported changes in patients with specific phobias to small animals who underwent a CBT exposure program and to prove if the CBT program made phobic patients process feared stimuli similarly to non-phobic persons.

Subjects and methods. The sample consisted of 32 adults, of which 16 (5 males and 11 females; mean age: 38.08) had specific phobia to small animals and 16 (4 males and 12 females; mean age: 21.81) had no phobias. A univariate before-and-after treatment design were used. In addition, the scores of the non-phobic group in self-reports and brain activity were compared with the post-treatment scores of the phobic group.

Results. Data show significant changes in brain activity, and improvements in self-reported measures because of applying CBT to specific phobias. As a highlight, participants showed a greater activation in points of the precuneus after receiving CBT. Also, when compared with non-phobic participants, phobic patients still remain with both fear and defensive responses to phobic stimuli.

Conclusions. The precuneus seems to be a regulator that reorganizes the processing of phobic stimuli. It can imply as CBT/exposure also active acceptance, self-awareness, and self-efficacy mechanisms.

Key words. Cognitive-behavior therapy. Exposure therapy. Functional magnetic resonance imaging. Parietal lobe. Precuneus. Specific phobia.

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Funding:
Ministry of Science, Innovation and Universities of Spain (projects PSI2013-42912-R and PSI2017-83222-R).

Accepted:
30.10.20.

How to cite this paper:
Viña C, Herrero M, Rivero F, Álvarez-Pérez Y, Fumero A, Bethencourt JM, et al. Changes in brain activity associated with cognitive-behavioral exposure therapy for specific phobias: searching for underlying mechanisms. Rev Neurol 2020; 71: 391-8. doi: 10.33588/rn.7111.2019487.

Versión española disponible en www.neurologia.com

Introduction

It is well established that psychological treatments can produce changes in behavioral patterns, belief systems and emotional regulation in humans. Cognitive-behavioral therapy (CBT) is currently the most effective psychological treatment for anxiety disorders and phobias, and exposure to feared stimuli is an essential component for CBT effectiveness [1-3]. There several models explaining the reasons of CBT/exposure efficacy [4], but two models seem to be better empirically supported: the emotional processing of fear model and the inhibitory learning model. In the emotional processing of fear model [5-7], the feared stimulus will (partially) lose its dangerous mental representation with repetitive exposure, changing the cognitive meaning of feared stimuli. However, in the inhibitory learning model [8,9], the original association learned during fear acquisition is not erased by new exposures to feared stimulus, but rather a new (inhibitory) response is acquired. It implies, among others, differences in stimulus processing, and these differences should be associated with changes in concomitant brain activity, implying functional changes in the brain areas that take part in the processing of feared stimuli [10-12].

It is expected that those mechanisms involve concomitant changes in the structure and functioning of the brain. Over the last decade, more than 500 neuroimaging studies have been conducted to analyze the neural bases of emotions and emotional regulation [13] provide consistent evidence of how changes produced by psychological treatment also imply morphological and functional brain changes [14-17]. Neuroimaging techniques are an objective resource for measuring the efficacy of psychotherapy and increasing our comprehension of the psychotherapy mechanisms implied in therapy efficacy [16-21].

Functional magnetic resonance imaging (fMRI) has shown differences in brain activity between phobic and non-phobic individuals in the processing of feared stimuli and also differences between different types of phobias [22-28]. Specifically, these studies agree on the importance of structures such as the insula, amygdala, pale globe, frontal cortex, thalamus and hippocampus, among others. Significantly, these findings are congruent with a dual-route functional network in processing feared stimuli: a unconscious route linking directly the thalamus with the amygdala; and a conscious route, involving the thalamus–sensory and association cortex–entorhinal, cortex–hippocampus–subiculum–amygdala [24,29-31].

Systematic reviews have pointed out the brain changes that occur in various mental disorders and psychological treatments [16,21]. These studies support the role of the insula, the amygdala, the prefrontal medial cortex and anterior cingulate gyrus in the acquisition and expression of fears and the efficacy of cognitive-behavioral therapy in the treatment of phobias using neuroimaging techniques [22-26]. According these data, and for anxiety disorders, a dual-process model of psychotherapy efficacy has been identify. Broadly, this model points out how psychological treatment efficacy implies an activation decrease in limbic areas, while prefrontal control areas activity is increased [32]. In general, this dual process has been observed in several studies, but, also, there have been observed some inconsistencies, especially related with the increase of prefrontal activation. On the other hand, a post-treatment precuneus activation have been found [33].

Because there still remain those inconsistencies, this study was conducted using fMRI to provide empirical support of brain activity changes because of the application of CBT/exposure to specific phobias. The main objectives were to assess the brain and self-reported changes in patients with specific phobias to small animals who had undergone a CBT exposure program and determine whether such changes were associated with brain functional changes. Finally, we intended to explore whether effective CBT makes phobic patients process feared stimuli similarly to non-phobic individuals.

Subjects and methods

Participants

The sample consisted of 32 adults, of which 16 (5 males and 11 females) had specific phobia to small animals (i.e., spiders, cockroaches and lizards) and 16 (4 males and 12 females) had no phobias. Because there is not sample standard for fMRI experimental studies for mental disorders, this study uses a sample size similar to those experimental studies on specific phobias [11,24,34,35]. The phobic group mean age was 38.08 years (SD = 11.55) and the non-phobic individuals were 21.81 years (SD = 5.19). There was a significant difference between the two groups in age ($t = 5.39$; $p < 0.001$). The following criteria had to be met to be included in the phobic group: being a small animal phobic adult; the phobia was a primary psychological disorder and not be explained by another health or psychological condition, not were receiving any treatment for the phobia, being right-handed with normal vision and no impediment to being subjected to an MRI session.

Instruments

The Composite International Diagnostic Interview (CIDI), version 2.1 [36] is a structured interview for the diagnosis of the main mental disorders according to the ICD-10 criteria [37]. Items/questions related to specific phobia, social phobia, agoraphobia and panic attacks were selected to corroborate the phobic diagnosis. In addition, in order to verify the inclusion criteria in the participants, a semi-structured interview was asked about each specific criterion. Participants diagnosed with a specific type of animal phobia (i.e., cockroaches, lizards and spiders) were included [37].

The Hamilton Anxiety Scale HAM-A [38] is a rating scale for clinicians that assesses the severity of patients' anxiety in 14 areas with a 5-point scale. It is a well-established scale with adequate psychometric properties, particularly regarding interjudge reliability as the intraclass correlation coefficients range from 0.74 to 0.96 [39]. A score of 14 or more on this scale was required in phobic participants.

The S-R (Situation-Response) Inventory of Anxiousness [40] is a 14-item inventory, 5-point Likert scale, that assesses the most frequent symptoms (i.e., physiological, cognitive and behavioral) associated with an anxious stimulus. The target phobic stimulus was point out prior to the participant's response. This instrument has high internal consistency (0.95) [40].

The Edinburgh Handedness Inventory [41] was used to determine participants were right-handed.

The nuclear magnetic resonance device used was a GE 3.0T Signa Excite HD. Because of phobic participants composed the sample and they could feel special discomfort inside the machine, fMRI ses-

sion time was reduced using an ASSET Calibration Method. This method for accelerating the acquisition of magnetic resonance imaging data, in the encoding phase, has made through parallel imaging technique that works by acquiring a reduced amount of *k*-space data.

Design

We used a univariate before-and-after treatment design in phobic individuals. The questionnaire scores and the brain image of the non-phobic group were compared with the after-treatment of the phobic group.

A block design was chosen to present the stimuli in the MRI device. fMRI sessions took around 10 minutes per participant. Each participant was randomly and alternately presented with 16 blocks of 20 seconds with images of the animal to which he/she had a phobia and 16 blocks of images of wooden balls as neutral stimulation. All the images had an identical white background. Participants were exposed to phobic and neutral stimuli with a 3D stereoscopic video with MRI-compatible 3D VisualStim digital glasses (graphic card: GeForce 8600GT).

The treatment program intended to eliminate the specific phobia to small animals was structured into eight sessions and was based on effective treatments justified by the evidence of the APA 12 Division Task Force [2]. This program included activities involving psychoeducation, physiological deactivation, cognitive restructuring, exposure, and relapse prevention. In the psychoeducational part, the cognitive-behavioral perspective on phobia was explained and patients were instructed on the principles of association (i.e., classical conditioning), the influence of consequences on behavior (i.e., operant conditioning), observation (i.e., vicarious learning) and thoughts (i.e., cognition). They were also trained in the management of subjective units of activation. Patients were given an explanation of why each of the other elements of the program was used, such as breathing (to control excessive physiological responses), cognitive restructuring (the seven most relevant cognitive distortions in phobias were treated) and therapist-guided exposure to video images of small animals (encouraging patients to undergo live exposure in the period between sessions), insisting that patients should keep focusing their attention on them. Relapse prevention was addressed in the last two sessions. The therapists were postgraduate psychology students who had been trained in the homogeneous application of the program.

Procedure

Phobic participants were recruited from April to July 2017 through different media (web pages, brochures, radio, local TV and newspapers). Specifically, individuals with phobia to small animals were invited to participate in an fMRI study. Participants would receive an 8-session psychological treatment for specific phobia, after their collaboration. Previously, participants signed the informed consent protocol. All participants had a diagnosis of specific phobia (according to the scores of the questionnaires), corroborated by the semi-structured interview. Only participants with non-removable metal devices such as implants were excluded due to their interference with the fMRI data collection. Non-phobic participants were recruited in a similar way among university students. Participants obtained course credit for their participation. Non-phobic participants were evaluated to ensure that they did not meet the criteria for a phobic disorder.

fMRI and data analyses

Psychological measures were compared using t-test analyses. Taking into account the proposal to lower the *p* value thresholds [42], a level of statistical significance of $p < 0.001$ was chosen for all analyses. Brain imaging was analyzed using Statistical Parametric Mapping software (SPM 12). The images were rendered and adjusted to the standard cerebral template of the Montreal Neurological Institute (MNI).

With regard to specific statistical analyses, a whole-brain study was carried out with hierarchical random effects as a general linear model. Intra and inter-group differences were tested with t-test analyses, using the SPSS statistical package. The age was introduced as a covariate, given there was a significant difference in this variable between phobic and non-phobic groups. For a voxel size of 4 × 4 × 4 mm, the activations selected were equal to or greater than a cluster size of three ($k \geq 3$, i.e. an activation volume of 192 mm^3). Again, an uncorrected $p < 0.001$ was considered in order to eliminate false positive results.

Results

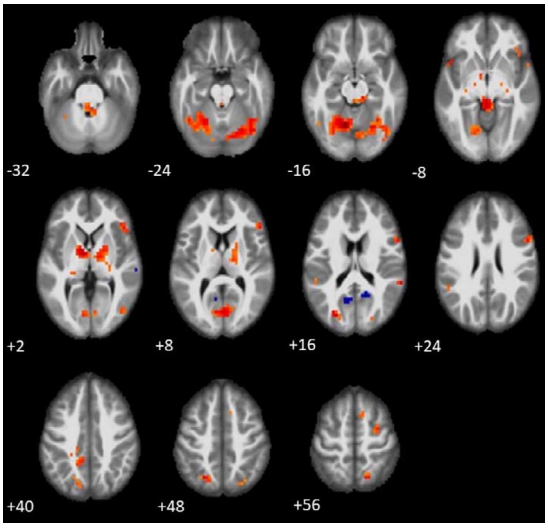
Self-report scales assessing specific anxiety associated with small animals in the phobic group before (S-R M = 38.38, SD = 6.72; HAM-A M = 16.47, SD = 9.22) and after the treatment (S-R M = 18.85, SD =

Table I. Pre- and post- treatment differences in the brain activity in the phobic group.

	Region	*k*	*t*	*x*	*y*	*z*
Pre > post	Cerebellum 6 L	160	7.04	–14	–60	–14
	Fusiform L	160	5.06	–34	–64	–18
	Thalamus L	36	6.06	–10	–4	2
	Cerebellar vermis (3)	58	5.85	–2	–36	–6
	Cerebellar vermis (10)	58	4.32	2	–44	–30
	Cerebellum 6 R	123	5.83	22	–68	–18
	Fusiform R	123	5.02	38	–56	–22
	Occipital inferior R	123	4.98	42	–80	–10
	Calcarine gyrus L	50	5.63	2	–76	10
	Occipital medium L	9	5.54	–26	–80	18
	Parietal superior L	27	5.31	–26	–64	50
	Frontal inferior orbital 2 R	25	5.23	38	24	–10
	Frontal inferior opercular R	16	4.86	54	12	26
	Parietal superior R	13	0.48	14	–68	54
	Thalamus R	69	4.67	22	–20	6
	Pallidum R	69	4.62	18	0	2
	Frontal superior 2 R	8	4.46	30	–4	58
	Precuneus L	10	4.45	–14	–44	42
	Occipital medium R	9	4.24	42	–76	2
	Thalamus L	7	4.17	–22	–28	–2
	Supramarginal L	9	4.15	–54	–44	26
	Supplementary motor area R	9	4.13	10	16	62
Post > pre	Precuneus L	12	4.67	–10	–60	14
	Precuneus R	7	4.53	14	–56	18

L: left; R: right. $p < 0.001$ uncorrected.

Figure 1. Pre- and post-treatment differences in the brain activity during phobic stimulation in the phobic group: pre > post (red) vs. post > pre (blue).



6.70; HAM-A M = 4.17, SD = 2.58) reached statistical significance with large effect sizes (S-R $t_{(30)} = 7.92$, $p < 0.001$, $d = 2.91$; HAM-A $t_{(30)} = 5.31$, $p < 0.001$, $d = 1.82$). The phobic anxiety scores of patients with a specific phobia had significantly decreased after treatment.

The comparisons between the pre- and post- treatment conditions of the phobic group in fMRI shows a significant decrease in brain activity (Table I). On the contrary, a significantly greater post-treatment activation was observed in the right and left precuneus. These changes and coordinates can be appreciated in figure 1.

In the comparison between phobic (S-R M = 18.85, SD = 6.70; HAM-A M = 4.17, SD = 2.58) and non-phobic (S-R M = 8.31, SD = 4.91; HAM-A M = 1.19, SD = 1.38) groups after treatment, the phobic group shows significantly higher scores in the two self-report measures with large effect sizes (S-R $t_{(30)} = 5.08$, $p < 0.001$, $d = 1.79$; HAM-A $t_{(30)} = 4.07$, $p < 0.001$, $d = 1.44$).

The fMRI comparisons between phobic and non-phobic groups after treatment shows that the phobic group had significantly higher brain activation in the precuneus and the insula (Table II). The differences between groups can be observed in figure 2.

Discussion

This study provide evidence that the use of a CBT can lead to changes in the brain activity of individuals with phobia to small animals. Results of com-

Figure 2. Post-treatment differences in the brain activity during phobic stimulation between phobic and non-phobic control group: phobic > control (red) vs. control > phobic (blue).

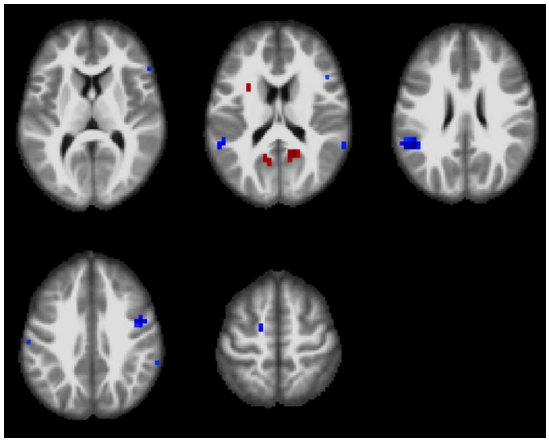


Table II. Post-treatment differences in the brain activity during phobic stimulation between phobic and non-phobic control group (ordered according to the t value).

	Region	*k*	*t*	*x*	*y*	*z*
Phobic > control	Precuneus R	10	3.97	14	–52	18
	Precuneus L	9	3.80	–10	–64	22
	Insula lobe L	3	3.72	–30	8	18
Control > phobic	Superior temporal gyrus L	32	5.82	–50	–44	26
	Precentral gyrus R	9	5.39	46	0	38
	Frontal superior 2 L	3	3.82	–18	–8	58
	IFG (*pars triangularis*) R	3	3.64	50	24	14
	Superior temporal gyrus R	6	3.64	62	–44	18

IFG: inferior frontal gyrus; L: left; R: right. $p < 0.001$ uncorrected.

paring before- and after- treatment measures in the phobic group showed less activation in multiple points of the brain and cerebellum after treatment. There was a decrease in activity in several parts of the thalamus, which is consistent with previous results [43], that found a reduced activity in the limbic and paralimbic areas because of a CBT. These data support the importance of the connectivity of the (para)limbic circuits for emotional deregulation in the pathological forms of fear [25].

The fMRI results showed that in spider phobics before CBT, the transient state of fear triggered by the phobogenic whereas the parahippocampal activation reflected an automatic reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of spider phobia. After successful completion of CBT, no significant activation was found in the lateral prefrontal cortex and the parahippocampal gyrus [15]. This data can be interpreted existing (but ineffective) voluntary regulation before therapy, disappears in the post-treatment, as it was no longer necessary. Increased activation in the insula and the anterior cingulate cortex is associated with specific phobia, whereas an attenuation of these brain responses correlates with successful therapeutic intervention [11]. This may assume the reduction of interoceptive distress after therapy is due the reduction of somatic anxiety, and it can suggests a lower need for anterior cingulate cortex regulation. Nonetheless, those data a closer to those studies which fail to find the dual process as a consequence of psychotherapy effects (diminishing limbic emotional areas activation, an increasing activation in prefrontal regulatory areas), as it has been proposed [32].

Interestingly, a greater activation was observed in the precuneus in participants after receiving CBT, as has been observed in previous studies [33]. This structure and the left insula also showed a greater activation in the phobic group after treatment compared to the non-phobic control group. The precuneus has been related to episodic memory, visuospatial processing, reflection and self-awareness, and the response to emotional stimuli [44,45]. It was found that the volume of gray matter on the back of the precuneus was positively correlated with self-efficacy and suggested that successful experiences contributing to self-efficacy also modify the anatomy of the precuneus [46]. Our results are consistent with this, as it is logical to expect that people who have overcome their phobia have increased their levels of self-efficacy with regard to their problem and therefore have increased precuneus activity. This is also consistent with the importance attributed to the role played by the precuneus in self-attributions [47].

By contrast, we observed a lower activation of the calcarine gyrus in the phobic group after treatment, which implies less functional activity of the primary visual area. This lower activation may indicate a reduction of the visual scrutiny of the phobic stimulus as an effect of the CBT. Moreover, the hemodynamic responses of the phobic group and the non-phobic control group when faced with phobic

stimuli response were different. In this regard, the concept of courage does not support but the concept of persistence despite fear (PDF) was proposed instead [48]. This concept is defined as the maintenance of behavior despite the subjective feeling of fear, as a more fruitful construct in the explanation of overcoming phobias. Although treatment program was not designed with the specific objective of increasing PDF, this may have been one of its achievements. One of the possible causes of this may be that the strategies used in the program (i.e., breathing control, cognitive restructuring, exposure) were not aimed at distracting the person from the feared stimulus but rather at making him/her concentrate completely on it. Therefore, when approach behaviors are fostered and reinforced, emphasizing the development of strategies to cope with the feared stimulus and persist in its presence, this facilitates the development of readiness to confront the feared situations. This can be understood as PDF according to the authors mentioned above and is likely to explain the differences found in the pattern of responses between both groups.

From a theoretical point of view, the results of this study support the effective role of conscious long route-processing model [30], and question the idea that exposure does not require higher-order cognitive functions to reduce fear responses [49]. Also these data have more consonances with the inhibitory learning model [8,9], than with the emotional processing of fear model [5-7]: despite psychological treatment significantly reduces anxiety levels, anxiety still remains (compared with healthy control group). Also, significant brain areas (as amygdala) still remain with relevant activation, as phobic stimuli are presented. This data suggest that initial fear responses were not replaced by a new adaptive response, but both responses happen together.

This study has several limitations. Although it had a sample size that is commonly used in this field, we believe that this is a limitation when generalizing the results. This type of studies should also be extended to other phobias to determine whether the brain activity of individuals treated for such phobias is similar. In the future, it would also be useful to include a phobic control group to explore the effect of the mere passage of time and to apply follow-up measures.

Future research should be aimed at improving treatment effectiveness. One way to achieve this would be by identifying predictive markers that can help assign patients to the optimal treatment according to their characteristics. This would reduce failure, chronification, lack of adherence, and minimize loss of time and expenses, both for the patient and the health system [50,51]. In this respect, it have been argued that the study of brain images is still in its infancy but that in the future the refinement of techniques for acquisition and analysis of functional and molecular neuroimaging data will help to improve treatments [15].

The results of the present study provide evidence of a well-known outcome: cognitive-behavior therapy is a valuable tool to deal with (specific) phobias. However, according to fMRI data, its effectiveness does not seem to lie as much in the reduction of fear and defensive responses (i.e., the amygdala and insula still showed considerable activity) as in the promotion of emotional regulation strategies and reflective self-awareness about phobia as an exaggerated fear (i.e., there was precuneus activation linked to the prefrontal cortex). Considering this, it might be useful for enhancing treatment effectiveness to add specific contents about fear acceptance, fostering self-perception consciousness and strengthening self-efficacy.

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Cambios en la actividad cerebral asociados a la terapia de exposición cognitivo-conductual para fobias específicas: búsqueda de los mecanismos subyacentes

Introducción. La evidencia disponible recoge resultados consistentes sobre cambios cerebrales morfológicos y funcionales producidos por el tratamiento psicológico. La terapia cognitivo-conductual (TCC) de exposición es actualmente el tratamiento psicológico más eficaz para las fobias.

Objetivos. Explorar los cambios cerebrales y autoinformados en pacientes con fobias específicas a animales pequeños sometidos a un programa de TCC de exposición y comprobar si el programa consiguió que estos pacientes procesaran los estímulos temidos de manera similar a las personas no fóbicas.

Sujetos y métodos. La muestra estuvo compuesta por 32 adultos, de los que 16 (5 hombres y 11 mujeres; edad media: 38,08 años) tenían un diagnóstico de fobia específica a animales pequeños y 16 (4 hombres y 12 mujeres; edad media: 21,81 años) no tenían dicho diagnóstico. Se utilizó un diseño univariado de tratamiento antes-después. Las puntuaciones del grupo sin fobia en autoinformes y activación cerebral se compararon con las puntuaciones del grupo con fobia posteriores al tratamiento.

Resultados. Los datos muestran cambios significativos en la actividad cerebral y mejoras en las medidas autoinformadas debido a la aplicación de la TCC a la fobia específica. Tras recibir TCC, los participantes mostraron una mayor activación en puntos del precúneo. Además, comparado con los participantes sin fobia, los pacientes fóbicos mantenían las respuestas defensivas y de miedo ante los estímulos fóbicos.

Conclusiones. El precúneo parece ser un regulador que reorganiza el procesamiento de los estímulos fóbicos. Puede implicar que la TCC de exposición, además, activa mecanismos de aceptación, autoconciencia y autoeficacia.

Palabras clave. Fobia específica. Imágenes de resonancia magnética funcional. Lóbulo parietal. Precúneo. Terapia cognitivo-conductual. Terapia de exposición.