Universidad Politécnica de Valencia

Programa de Doctorado Tecnologías para la Salud y el Bienestar

UNIVERSIDAD POLITECNICA DE VALENCIA

PhD Thesis

Contributions to Neuropsychotherapy of the Combined Use of Neuroimaging and Virtual Exposure for Assessment in Psychological Treatments.

Miriam Clemente Bellido

PhD Advisors:
Beatriz Rey Solaz
Mariano Alcañiz Raya

Valencia, April 2014

A mis padres, sin cuyo apoyo esta Tesis no habría sido posible, y que nunca tiraron la toalla conmigo

Resumen

La neuropsicoterapia es una nueva filosofía adoptada en el tratamiento de trastornos mentales, que basa sus principios en la aplicación de la información conocida sobre las activaciones cerebrales y el funcionamiento del cerebro para ajustar la terapia, de cara a enfocar el proceso en función de cómo el cerebro evoluciona hacia activaciones consideradas normales. Las nuevas herramientas aparecidas en el campo de la neuroimagen han ayudado en este proceso, proveyendo de información detallada y precisa sobre el funcionamiento del cerebro de cada paciente en particular. De entre las muchas técnicas de neuroimagen disponibles hoy en día, la resonancia magnética funcional (fMRI) destaca por su alta resolución espacial, lo que permite un mayor conocimiento sobre qué áreas se activan ante cada estímulo o están envueltas en la realización de cada acción. Las desventajas que esta técnica presenta en términos de tamaño del escáner y restricción de movimiento dentro del mismo dan pie a la distinción de otra técnica, más apropiada en ciertos casos: la electroencefalografía (EEG), que permite una mayor libertad de movimientos y provee de una mayor resolución temporal.

Para los intereses de esta Tesis, ambas técnicas serán comparadas, con el fin de obtener cuál de ellas ofrece mayores beneficios. Para ello, un nuevo factor será tenido en cuenta. Debido a las limitaciones de las técnicas de neuroimagen en torno a la presentación de los estímulos, hay ciertas situaciones de la vida real a las que no podemos exponer a los sujetos. Aquí es donde la realidad virtual (RV) entra en escena. Gracias a la RV somos capaces de trasladar al sujeto a un mundo virtual donde cualquier tipo de estímulo es posible. En el caso de la neuropsicoterapia, esto permitirá la exposición del paciente a situaciones relacionadas con su desorden, de un modo controlado y más seguro.

De hecho, la realidad virtual ha sido ampliamente utilizada en el tratamiento de trastornos psicológicos; sin embargo, hasta ahora no ha sido aplicada durante la evaluación de la enfermedad. Para los

objetivos de esta Tesis, los entornos virtuales serán usados para la evaluación de sujetos antes y después de pasar por un tratamiento psicológico para su trastorno específico, usando técnicas de neuroimagen como herramienta para obtener información útil que pueda ayudar en el proceso terapéutico. Como ejemplo de trastorno, se ha elegido la fobia a animales pequeños (en concreto, a arañas y cucarachas), aunque las conclusiones de este estudio son extrapolables a otro tipo de desordenes psicológicos.

Antes de ser capaces de asegurar que las activaciones cerebrales obtenidas son debidas al trastorno y no a otras variables, es necesario medir el sentido de presencia que los sujetos sienten durante la experiencia virtual. Esta es la razón por la que se incluyó, previamente al estudio de la evaluación de un trastorno psicológico, un estudio del sentido de presencia en un entorno virtual. Dicho estudio también ayudó en la decisión de qué técnica de neuroimagen es más apropiada para llevar a cabo la segunda parte de la Tesis. Tanto EEG como fMRI fueron usadas para la medida de presencia en el mismo entorno virtual, y los resultados en términos de activaciones cerebrales fueron comparados. La presencia fue también medida por medio de cuestionarios, la forma subjetiva tradicional de medirla. Como resultado de este estudio, se esperaba comprobar si la RV podía efectivamente estimular el sentido de presencia y decidir qué técnica de neuroimagen era más apropiada para los objetivos de la Tesis.

Para resumir, las hipótesis iniciales de esta Tesis fueron:

1- Las nuevas técnicas de neuroimagen pueden proveer información útil para la neuropsicoterapia.

2- La realidad virtual puede ayudar en la evaluación del trastorno, mejorando la exactitud con la que los sujetos son expuestos al estímulo.

3- Los entornos usados serán lo suficientemente envolventes como para que el paciente se sienta presente en ellos y los considere "reales".

Para lograr dichos objetivos, cada una de las líneas de actuación planteadas (estudio de presencia y evaluación de un trastorno mental) se dividió a la vez en dos partes. En total, se desarrollaron cuatro estudios:

1- Estudio del sentido de presencia en entorno virtual mediante fMRI: el objetivo de esta parte de la Tesis fue comprobar si los entornos eran capaces de estimular el sentido de presencia, correlando los resultados con los datos obtenidos por medio de cuestionarios.

2- Estudio del sentido de presencia en entorno virtual mediante EEG: el objetivo aquí fue comparar las activaciones cerebrales obtenidas mediante EEG con aquellas obtenidas en el primer estudio, a la vez que comprobar que las respuestas a cuestionarios fueron equivalentes, a pesar de la menor intrusividad del escáner.

Como resultado de estos dos estudios, se decidió que los entornos eran suficientemente envolventes como para inducir el sentido de presencia, y que la mejor técnica de neuroimagen a utilizar para la segunda parte de la Tesis era la fMRI, debido a su mayor resolución espacial.

3- Evaluación de trastorno psicológico, pre-tratamiento: una vez decidido que el estudio se llevará a cabo usando fMRI, las áreas relacionadas con el trastorno mental escogido (fobia a animales pequeños) se estudiaron usando RV como estímulo. Hasta la fecha, la evaluación de dicho trastorno se había realizado usando imágenes o vídeos de animales reales como estímulo, pero no usando RV; lo que se hipotetiza que permitirá un mejor acercamiento a la experiencia fóbica.

4- Evaluación del estado de sujetos con desorden psicológico, post-tratamiento: una vez los pacientes han pasado por un tratamiento

para curar la fobia, fueron evaluados otra vez para comprobar si las áreas cerebrales relativas a la fobia dejaban de activarse después de la terapia.

Como resultado de esta segunda parte de la Tesis, se obtuvieron las áreas relativas a la fobia (que dejaban de activarse tras el tratamiento). Se espera que dicha información pueda ser útil en futuros trabajos de neuropsicoterapia para conseguir un mejor ajuste del trastorno.

En conclusión, con esta tesis se han conseguido estudiar las ventajas que las nuevas técnicas de neuroimagen y la realidad virtual pueden proveer en el campo de la neuropsicoterapia.

Abstract

Neuropsychotherapy is a new philosophy in the treatment of mental disorders that bases its principles in the application of the information we have about the brain activations and brain functioning to adjust the therapy to them, in order to center the process in how the brain evolves to its normal activations. New tools in the field of neuroimaging have helped in this process, providing accurate and detailed information about how the particular brain of each patient works. Between the many neuroimaging techniques available nowadays, the functional magnetic resonance (fMRI) stands out by its high spatial resolution, which allows a better knowledge of which brain area is activated before each stimulus or while performing each activity. The disadvantages this technique presents in terms of size of the scanner and restriction of movements give light to another technique, more suitable in certain domains: the electroencephalography (EEG), which provides a greater freedom of movement and higher temporal resolution.

For the purposes of this PhD Thesis, both techniques will be compared, in order to find which one better suits our interests. For doing so, another factor will be taken into account. Due to the limitations the neuroimaging techniques have in terms of presentation of the stimuli, we are not able to expose the subject to certain kinds of real life situations. There is where the virtual reality (VR) enters the scene. With VR we are able to move the subject to a virtual world where any kind of stimulus is possible. In the case of neuropsychotherapy, it will allow the exposition of the patient to a situation related to his disorder, in a safer and more controlled environment.

In fact, virtual reality has been widely used for the treatment of psychological disorders; but, until now, it has not been applied during the assessment of the disease. For the aims of this Thesis, virtual environments will be used for the assessment of subjects before and after undergoing a psychological treatment for a specific disorder,

using neuroimaging techniques to find useful information that could help during the therapeutic process. As an example of disorder, the phobia to small animals (spiders and cockroaches) has been chosen, although the conclusions of this study could be extended to other kinds of psychological disorders.

Before being able to assure that the brain activations obtained are related to the disorder and not to other issues, it is needed to measure the sense of presence the subjects felt during the virtual experience. This is why before the assessment of a psychological disorder, a study of the sense of presence in a virtual environment was introduced. This study also helped in the decision of which neuroimaging technique apply in the second part of the Thesis. EEG and fMRI were used for the measure of presence in the same virtual environments, and the results in terms of brain activations were compared. Presence was also measured by means of questionnaires, the traditional subjective way of measuring it. As a result of this study it is expected to check if VR could effectively stimulate presence and which neuroimaging technique is more appropriate for the targets of this Thesis.

To sum up, the initial hypotheses of this Thesis are that:

1- The new neuroimaging techniques can provide of useful information to use during neuropsychotherapy.

2- Virtual reality would help in the assessment of the disorder, improving the accuracy in the way the subjects are exposed to the stimuli.

3- The environments used would be immersive enough so the patient will feel present in them and feel them as real.

For fulfilling these objectives, each of the two courses of work (study of presence and assessment of a mental disorder) was divided in two parts. In total, four studies were developed:

1- Study of the sense of presence in a virtual environment using fMRI: the aim of this part of the Thesis was to check if the environments were able to stimulate the sense of presence, correlating the results with those given to questionnaires.

2- Study of the sense of presence in a virtual environment using EEG: the aim here was to compare the brain activations obtained with EEG with those from the previous study, and if the responses of the questionnaires were equivalent despite being in a less intrusive scanner.

As a result of these two studies, it was decided that the environments were immersive enough to induce the sense of presence, and that the best neuroimaging technique for the next part of the Thesis was the fMRI, due to the higher spatial resolution it brought.

3- Assessment of a psychological disorder, pre-treatment: once decided the study will continue with fMRI, the areas related to a specific disorder (small animals' phobia) were studied using VR as stimulus. Until now, the assessment has been done using real animals as stimuli but not using VR, which here is hypothesized to allow a better approach to the phobic experience than the view of photographs or videos of real animals.

4- Assessment of the state of subjects with a psychological disorder, post-treatment: once the patients had underwent a treatment to cure the disorder, they were assessed again to check if the brain areas related to the phobia stopped being activated after it.

As a result of this second part of the Thesis, the brain areas related to the phobia (that stopped being activated after the treatment) were obtained, and this information is hoped to be useful in future neuropsychotherapeutic works, for the better adjustment of the disorder.

In conclusion, this PhD Thesis studies the advantages that the new neuroimaging techniques and virtual reality could bring to the study of neuropsychotherapy.

Resum

La neuropsicoteràpia es una nova filosofia que s'ha adoptat durant el tractament de malalties mentals, basada en l'aplicació de la informació coneguda sobre les activacions cerebrals i el funcionament del cervell per ajustar la teràpia, de cara a enfocar el procés en funció de com evoluciona el cervell cap a les activacions considerades normals. Les noves ferramentes aparegudes en el camp de la neuroimage han ajudat en aquest procés, proveint informació detallada i precisa del funcionament del cervell en cada pacient particular. Entre les moltes tècniques de neuroimagen disponibles hui en dia, la ressonància magnètica funcional (fMRI) destaca per la seua alta resolució espacial, que permet un major coneixement de què àrees s'activen amb cada estímul o estan envoltes en la realització de cada acció. Els desavantatges que aquesta tècnica presenta en termes de grandària de l'escàner i restricció del moviment dins del mateix donen peu a la distinció d'una altra tècnica, més apropiada en certs casos: l'electroencefalografia (EEG), que permet una major llibertat de moviment i té una major resolució temporal.

Per als interessos de la Tesi, les dos tècniques es compararan, de cara a obtindre quina ofereix majors beneficis. A més, un altre factor serà tingut en compte. Les limitacions que les tècniques de neuroimage tenen al voltant de la presentació d'estímuls fa que hi hagen certes situacions de la vida real que no es poden mostrar als subjectes. En aquest punt es on la realitat virtual (RV) entra en joc. Gràcies a la RV som capaços de traslladar el subjecte a un món virtual on qualsevol tipus d'estímul és possible. En el cas de la neuropsicoteràpia, aquest ens permetrà l'exposició del pacient a situacions relacionades amb la seua malaltia, de un mode controlat i més segur.

De fet, la realitat virtual ha sigut àmpliament utilitzada en el tractament de trastorns psicològics; no obstant, fins ara no ha sigut aplicada durant la avaluació de la malaltia. Per als objectius d'aquesta Tesi, els entorns virtuals seran usats per a l'avaluació de

subjectes abans i després de passar per un tractament psicològic per al trastorn específic, utilitzant tècniques de neuroimage com a ferramenta per obtindre informació útil que puga ajudar en el procés terapèutic. Com exemple de malaltia, es va elegir la fòbia a animals petits (en concret, a aranyes i paneroles), encara que les conclusions d'aquest estudi són extensibles a altres tipus de trastorns psicològics.

Abans de ser capaços d'assegurar que les activacions cerebrals obtingudes son degudes a la malaltia i no a altres variables, es precís mesurar el sentit de presencia que els subjectes senten durant l'experiència virtual. Aquesta es la raó per la que es va incloure, prèviament al estudi de la avaluació d'un trastorn psicològic, el estudi del sentit de presencia en un entorn virtual. Dit estudi també va ajudar en la decisió de quina tècnica de neuroimagen era la més adequada per a la segona part de la Tesi. Tant EEG com fMRI van ser utilitzades per a la mesura de presencia en el mateix entorn virtual, i els resultats en termes de activacions cerebrals van ser comparats. La presencia va ser mesurada també mitjançant qüestionaris, que es la manera tradicional per a la seua mesura. Com a resultat de l'estudi, s'esperava comprovar si la RV podia efectivament estimular el sentit de presencia i decidir quina tècnica de neuroimage era la més adequada per als objectius de la Tesi.

Com a resum, les hipòtesi inicials d'aquesta Tesi van ser:

1- Les noves tècniques de neuroimagen poden proveir d'informació útil per a la neuropsicoteràpia.

2- La realitat virtual pot ajudar en l'avaluació del trastorn, millorant l'exactitud amb la qual els subjectes són exposats a l'estímul.

3- Els entorns utilitzats seran suficientment envoltants per aconseguir que el pacient es senta present en ells i els considere "reals".

Per a aconseguir aquests objectius, cadascuna de les dues línies d'actuació (estudi de presencia i avaluació d'una malaltia mental) es

va dividir a la mateixa vegada en dues parts. En total, es van desenvolupar quatre estudis:

1- Estudi del sentit de presencia en entorns virtual mitjançant fMRI: l'objectiu va ser comprovar si els entorns virtuals eren capaços d'estimular el sentit de presencia, correlant els resultats amb els obtinguts dels qüestionaris.

2- Estudi del sentit de presencia en entorn virtual mitjançant EEG: l'objectiu en aquesta part de la Tesi va ser comparar les activacions cerebrals obtingudes amb EEG amb les obtingudes en el primer estudi, i al mateix temps comprovar que les respostes a qüestionaris eren equivalents, a pesar de la menor intrusivitat de l'escàner.

Com a resultat d'aquests dos estudis, es va decidir que els entorns eren suficientment envoltants com per a induir el sentit de presencia, i que la millor tècnica de neuroimage a utilitzar per a la segona part de la Tesi era la fMRI, a causa de la seua millor resolució espacial.

3- Avaluació de trastorn psicològic, pretractament: una vegada que s'ha decidit que l'estudi es desenvoluparà utilitzant fMRI, les àrees relacionades amb la malaltia triada (fòbia a animals petits) es van estudiar utilitzant RV com estímul. Fins ara, l'avaluació del dit trastorn s'havia realitzat usant imatges o vídeos d'animals reals com a estímul, però no usant RV; la qual cosa s'hipotetitza que permetrà un millor acostament a l'experiència fòbica.

4- Avaluació de l'estat de subjectes amb trastorn psicològic, post-tractament: una vegada els pacients han passat per un tractament per a curar la fòbia, van ser avaluats una altra vegada per comprovar si les àrees cerebrals relatives a la fòbia deixaven d'activar-se després de la teràpia.

Com resultat d'aquesta segona part de la Tesi, les àrees relatives a la fòbia (que deixaven d'activar-se després del tractament) van ser obtingudes, i s'espera que la dita informació puga ser útil en futurs treballs de neuropsicoteràpia per un millor ajustament del trastorn.

En conclusió, en aquesta Tesi s'han estudiat els avantatges que les noves tècniques de neuroimage i la realitat virtual poden proveir en el camp de la neuropsicoteràpia.

Contents

1 Introduction

In the study of the brain, many are the efforts done to try to understand its precise function. The great development of the new neuroimaging techniques are an example of these efforts. Brain imaging methods such as fMRI, PET or EEG have improved their ways of capturing and processing the images in order to extract more relevant and useful information from the brain scans. More precisely, the functional magnetic resonance image technique (fMRI) is widely used due to its great spatial resolution (between 1 and 3 mm) and its good temporal resolution of about 1s (Baumann et al., 2003). However, the fMRI is highly invasive (when the participants are inside the fMRI they are completely limited, and all the stimuli that the subjects can receive are reproduced by adapted glasses or headphones); so when a higher freedom of movements is required, the electroencephalography (EEG) is the chosen one. Moreover, the EEG presents the additional advantage of having a temporal resolution of milliseconds.

One tool that has helped in overcoming the disadvantages due to the limitations in movement during the scan is virtual reality (VR). With virtual environments, you can move the subject to any situation you want him to face, and still be able to measure his brain activity during tasks he would not be able to perform inside the fMRI in any other way. Moreover, the situations in which he is introduced are completely controlled, so there will be no risks for him (which is especially useful, for example, when applying VR for the treatment of psychological disorders).

The present PhD Thesis was conducted in the *LabHuman* group (I3BH) inside the *Universitat Politècnica de València* (UPV), supported by the *Generalitat Valenciana* under a VALi+d Grant. The research was conducted in collaboration with the *Labpsitec* group and the *Departamento de Psicología Básica, Clínica y Psicobiología* from the *Universitat Jaume I* in Castellón. LabHuman has wide experience in the use of Virtual Reality for different purposes. Moreover, it has

previous experience in the study of the sense of presence using a brain activity technique, Transcraneal Doppler (TCD), for its measure (work developed in the PhD Thesis of Beatriz Rey directed by Mariano Alcañiz).

In the present work, the main goal was to study the possibilities of the combined use of virtual reality with neuroimaging in the field of neuropsychotherapy. For this purpose, the course of action was divided into two main objectives: the study of the sense of presence inside a virtual environment and the assessment of the effects that a psychological treatment to cure a mental disorder (in particular, small animals' phobia) has over the brain activations of the subjects, using virtual environments as stimuli. Before being able to assess or treat a mental disorder by means of virtual reality, it is needed to make sure that the environment elicits the sense of presence in the subject (Bush, 2008; Vincelli & Riva, 2002). That is why in the first place neuroimaging techniques were used to analyze the brain areas activated while feeling present in the virtual world. Moreover, the aim was to check by means of questionnaires if the subject felt present despite the interference introduced by the neuroimaging devices (the fMRI scanner or the EEG headset). Because the EEG device is clearly less invasive than the fMRI scanner, both neuroimaging techniques were compared to see if the virtual experience was influenced by that. In fact, fMRI results were compared with those obtained with a wireless portable EEG Emotiv EPOC, which allows an even higher freedom in the user and is easier to put on. With this the intention was to evaluate if the brain areas related to the sense of presence activated were equivalent whatever technique was used, and that the virtual experience was not influenced by the neuroimaging technique used. This also helped in the choice of the neuroimaging technique more appropriate for the second phase of the study, in which the effects of the psychological treatment were studied using virtual environments as stimuli. Finally, it was decided that the technique with the greater spatial resolution (the fMRI) was the most advisable for the interests of the Thesis.

1.1 Objectives

To delve into the applications of virtual reality and neuroscience in the neuropsychotherapy, as aforementioned, the study was divided into two courses of action: the study of presence and the assessment of a psychological treatment (study of small animals' phobia). Presence is the feeling the subject has of "being there", inside the virtual environment, although his body is located elsewhere (Sheridan et al., 1992). Since the feeling of presence is fundamental in any study developed with VR, for measuring the brain areas related with the phobia while exposing the patient to a virtual environment, first it is needed to ensure that the subject feels the environment as real. So both courses of the research are closely related. Now there will be described the different achievements to reach in this work.

1.1.1 Evaluating Presence in a Virtual Environment

In this study the first objective will be to analyze the sense of presence the subject feels while navigating through a virtual environment. For this, three experimental conditions will be compared: view of photographs, view of a video of an automatic navigation and free navigation in the VE. In all parts of the study, the subjects will fulfill some presence questionnaires which will provide a subjective measure of their sense of presence that will be compared with the results obtained in terms of brain activation. The questionnaires used were the SUS questionnaires (Usoh et al., 2000), developed to evaluate the sense of presence *a posteriori*. Those tests consisted in six 7-point Likert type questions, to answer depending on the strength of the presence experienced (see Appendix 4).

This study is first developed with fMRI to check if it is really possible for the subject to feel present while being laid down inside the scanner. To verify these results, they will be compared with those obtained in an equivalent EEG research. In this one, the subjects perform the same task, but this time with a less influential

neuroimaging machine such as the EEG helmet. The intention was to check if the results obtained with both techniques were comparable.

Moreover, inside the EEG study another objective was considered. A new kind of EEG helmet has been recently released, which allows an easier placement of the electrodes and is portable and wireless. This helmet is much cheaper and easy to work with, so the activations obtained with this new helmet (Emotiv EPOC, Emotiv Systems, Eveleigh, Sydney, Australia) will be compared with those obtained with the fMRI scan, and check the usability of the device for scientific research.

To summarize, the objectives in this section will be:

- To check if the presence experience inside a virtual environment can be elicited, even inside a fMRI scan, where the subject has to remain laid down and the situation is uncomfortable to him.

- To measure the differences in brain activation between the three navigation conditions: photographs, video and navigation. These comparisons will lead to three groups of results. The comparison between the navigation and video conditions obtains the brain activations due to the free movement through the environment, avoiding any other constituent. The comparison of the navigation and photographs conditions obtains the activations for the navigation condition, using as control still images which avoid activations due to visual stimuli, but still maintain those related to the visual movement through the VE. Lastly, the comparison of the video and photographs conditions only considers the guided movement in comparison with still photographs.

- To compare those fMRI results with the answers given by three post-scan presence questionnaires (one for each condition). This will lead to the measure of the correlations between the brain activations and the subjective ratings of presence.

- To compare the results given to the presence questionnaires in the fMRI study with those obtained in a previous TCD research conducted by the Labhuman group (Alcañiz et al., 2009).

- To measure the differences in brain activation between the same three experimental conditions with a high temporal-resolution technique such as EEG. For obtaining the brain activations out of the electrical signals of the scalp, sLORETA tool will be used.

- To compare between the brain activations obtained from the EEG signals and those obtained with a high spatial-resolution technique such as fMRI.

- To compare the results given to the presence questionnaires in the EEG study to those obtained in the fMRI study.

- To evaluate the usefulness of the Emotiv EPOC for the research field. This headset, although designed for more commercial applications such as games, could save time and money if demonstrated its functioning in the research area. Not only this device costs far less than any other neuroimaging scan, but also its placement over the scalp takes only a few minutes, in comparison with the half an hour needed for other EEG devices.

At the end of this study, the global objective would be to evaluate the usefulness of the neuroimaging techniques for the measure of

presence, giving more objective results than the traditional questionnaires; and allowing the monitoring of the sense of presence over time and in terms of brain activations.

Moreover, the proof of the sense of presence being elicited inside a fMRI scan will allow the development of the second course of study of this PhD Thesis: the assessment of the effects of a psychological treatment over the brain activations, using fMRI. If it can be proved than the subjects feel presence inside the VE although being laid inside a fMRI scan, then it can be assured that the brain areas activated during the assessment are due to the phobia and not to other causes; because if the subject feels he is present in the fMRI setting, he would react to the phobic objects as he would do in the real world.

1.1.2 Assessment of a psychological treatment

The second curse of investigation will cover the contributions that the neuroimaging assessment of the effects of a psychological treatment over the brain activations may have over the neuropsychotherapeutical theory, and how the information obtained from this kind of studies can be used in the benefit of the treatment of a psychological disorder. All this was developed for one specific kind of disorder: the small animals' phobia, more specifically, the spiders and cockroaches' phobia. Until now, Virtual Reality has been widely used for the treatment of phobias, but not as stimuli for the assessment of the phobic subjects. In this study, entirely performed with fMRI, two scans will be applied to each subject. Each patient will be scanned before and after going on a psychological treatment to get over the phobia, and the brain areas activated in both scans will be compared.

During the scan, the task the subjects have to perform is divided in three conditions: navigation through a clean room (clean), navigation through a dirty room but without spiders or cockroaches (dirty) and navigation through a dirty room with the phobic animals (phobic). So in the results' analysis there will be three comparisons to analyze: in

the first one the phobic and dirty conditions will be compared, which will provide of information about the brain activations related to the fear without considering the anxiety level; in the second one a comparison between the phobic condition and the clean one will be done, taking into account all the brain activations related to the phobia (fear and anxiety); and finally the third one, the comparison between the dirty and the clean conditions, will measure the anxiety levels in the subject when he sees a room susceptible to have spiders and cockroaches, but without them (anxiety due to the dirtiness of the room).

Altogether, the specific objectives of this curse of the research will be:

- Analyze the brain areas related to the phobia in the three aforementioned comparisons. Those results correspond to those obtained in the pre-treatment fMRI scan conducted over the phobic subjects.

- Compare the activations obtained in this study using VR as stimuli with those obtained in previous researches conducted by other groups, using images of real animals.

- Obtain the brain areas activated in the phobic subjects after the psychological treatment has been applied. Compare those with the ones obtained before the treatment and evaluate if those activations that were identified as related to the phobia in the pre-scan are no longer activated.

- Obtain the brain areas which had a restrained activation caused by the phobia, and after the treatment were reactivated.

As a result of this study, the hypothesis of the usefulness of virtual reality to the phobia stimulation during the assessment of the

disorder will be analyzed. This would open the door for the use of virtual stimulus instead of real ones during the assessment of the phobias. This would help, for example, in the analysis of mild phobic subjects, whose fear is not activated with the simple use of pictures and need more stimulating stimuli such as virtual environments. What is more, those environments allow the personalization of the characteristics for adjusting the level of phobia of the subject, and always in a safe surrounding. In the case of small animals' phobia, this allows the assessment of the patient in medical installations, where the introduction of real animals could need for special permissions. In other cases where the phobia-related anxiety is difficult to be elicited from a clinical environment, such as agoraphobia or fear of flying, the VR could allow the assessment avoiding the direct exposure of the patient to the real situation.

As a more general goal, the information obtained in this section would show the possibilities that neuroimaging and virtual reality could bring to neuropsychotherapy. In the future, this could lead to the adaptation of the therapy to incorporate the information in terms of brain areas for the better treatment of the patient.

1.2 Structure

The present document is organized in the following chapters:

- CHAPTER 1: Introduction. This current chapter covers the introduction to the study conducted in this PhD Thesis, as well as the objectives fulfilled. In the first section it has been described the motivation and content of the thesis, as well as the different studies conducted. In the second part the objectives were described. In this third part, a description of the different chapters of this document is being fulfilled.

- CHAPTER 2: Neuropsychotherapy. In this theoretical chapter, the justification of this PhD in terms of the neuropsychotherapeutical theory will be presented, as well

as the previous knowledge needed for the better understanding of this work. First, there will be explained in detail the main characteristics of the brain, its functioning and structure. This will bring a better understanding of it before explaining what has been done in this PhD Thesis. Then, the two neuroimaging techniques used (fMRI and EEG) will be explained: its historical development, its functioning, its applications and the analysis of the data. Finally, the proposal of work for this thesis will be exposed, which will describe the underpinnings of the virtual reality and a little state of the art of the work previously done.

- CHAPTER 3: Presence. In the third chapter, the study about measuring the sense of presence felt while navigating inside a virtual environment will be exposed. First, the definition of presence inside a virtual environment will be explained, and the different ways of measuring presence used until now presented. Once the theory has been exposed, there will be explained the two studies developed in this PhD Thesis for the measure of presence. First, there will be described the virtual environments used, that were the same for the two studies. Then, the fMRI study of the sense of presence will be presented, indicating the subjects that underwent the scans, the questionnaires they fulfilled, and the parameters used for acquiring the images (Materials and Methods section). Then, the results obtained for each of the experimental conditions will be presented, as well as the comparisons with the questionnaires (Results section). Finally, a discussion of those results will be done (Discussion of the Results section).

  After presenting the fMRI study, it will be exposed the work conducted using EEG to check if the results were equivalent to those obtained using fMRI. It will be explained the subjects that were analyzed, how the data were taken and the

questionnaires fulfilled. This study was developed with two different screens: a power wall and a desktop screen. These two devices will be described and, then, the results obtained with each one will be presented and discussed, comparing the data of the two studies and comparing them with the results obtained in the fMRI work.

- CHAPTER 4: Assessment of a treatment: Small Animals' Phobia. In this chapter, the study of small animals' phobias will be exposed. First, an introduction to the phobia will be done: the spread and main characteristics of this mental disorder, the traditional ways of assessing the phobic subjects and how the use of neuroimaging techniques combined with VR could help, and the principal ways of treating the disorder. Then, the study conducted will be presented. First there will be introduced the Materials and Methods section, where there will be explained the subjects that were scanned, the environments used, the fMRI procedures developed and the analysis of the data. Next, the Results for the pre-treatment study will be presented and discussed. The same will be done for the comparison between the pre-treatment and the post-treatment results. Finally, the overall conclusions of the study will be explained and the limitations discussed.

- CHAPTER 5: Conclusions. In this final chapter, the main conclusions of the two branches of study will be presented, and the future lines of work exposed. The conclusions of the presence study will cover the usefulness of neuroimaging techniques for the measure of the sense of presence, the advantages and disadvantages to use fMRI vs. EEG and the possibilities the low-resolution Emotiv EPOC EEG headset could offer. The conclusions of the assessment of a treatment study will include the correspondence between

the brain areas activated in this research and those obtained in previous works using real animals as stimuli and the possibilities the use of virtual reality for the assessment of small animals' phobia could bring. Finally, all these specific conclusions from each branch of study will be taken into account together to originate the overall conclusions of this thesis and the contributions that neuroimaging and virtual reality could bring to neuropsychotherapy.

In this chapter there will also be included the publications derived from the work developed in this PhD Thesis. Finally, the main future curses of investigation to lead and the possible future studies will be exposed.

- APPENDIXES. Finally, 6 appendixes have been included:
    1. Appendix 1: The informed consent the subjects have to sign before entering the fMRI scan.

    2. Appendix 2: The informed consent the subjects have to sign before passing the EEG scan.

    3. Appendix 3: The "Edinburg Handedness Inventory" (Oldfield et al., 1971) questionnaire to measure the laterality over the participants of the study.

    4. Appendix 4: The SUS questionnaires (Usoh et al., 2000) used for the subjective measure of presence, personalized for each of the experimental conditions: photographs, video and navigation.

    5. Appendix 5: The diagnostic criteria (DSM-IV) for 300.29 specific phobia.

6. Appendix 6: The Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) for the specific phobias, a semistructured model of interview for the assessment of the phobia.

2 Neuropsychotherapy

Before presenting the studies that were conducted for this thesis, it is necessary to introduce the background in which the work was set. The main hypothesis of this Thesis recalls in the assessment of the changes produced in the brain due to a psychological treatment. More specifically, the comparison between the brain activations before and after the treatment will show the changes produced following a characteristic of the brain called neuroplasticity. Until now, many studies have been benefited by the goodness of the use of virtual reality during the treatment itself. However, this same virtual reality has not been applied for the assessment of the effects of this treatment.

In the treatment of mental disorders, a new course of study has appeared that defends the hypothesis that psychological therapies could be improved by making use of the knowledge acquired about the brain functioning, changing the way in which the treatment is applied to match the brain activity patterns pursued. According to this, a more accurate knowledge of the patient's specific brain functioning would help in modeling his treatment according to his needs.

Before entering in more detail in the matter of the work developed in this Thesis, the theoretical basis in which it has been based will be introduced. First of all, a brief explanation of the brain and its structure will be made. Then, the principles of neuropsychotherapy will be exposed. For the better understanding of the brain functioning, some tools are needed to analyze it. This is where the neuroimaging techniques come into play. Finally, as aforementioned, the proposal of the use of virtual environments instead of real ones for the assessment of the treatment's effects will be done, together with a brief introduction to the virtual reality.

2.1 The Brain

Let's situate the brain inside the body, as a fundamental part of the nervous system. The nervous system is the part of the body charged with the coordination of all the voluntary and involuntary actions, communicating all the areas of the body. The human nervous system is divided in two main areas: the central nervous system (CNS) and the peripheral nervous system (PNS). The peripheral nervous system is formed by all the nerves that go across the body, transmitting the senses and orders from/to the CNS. The CNS is formed by the encephalon and the spinal cord, and protected by the meninges. The encephalon is formed at the same time by the brain, the cerebellum (located below the brain, in its posterior area) and the brainstem (which connects the brain with the spinal cord), and protected by the skull.

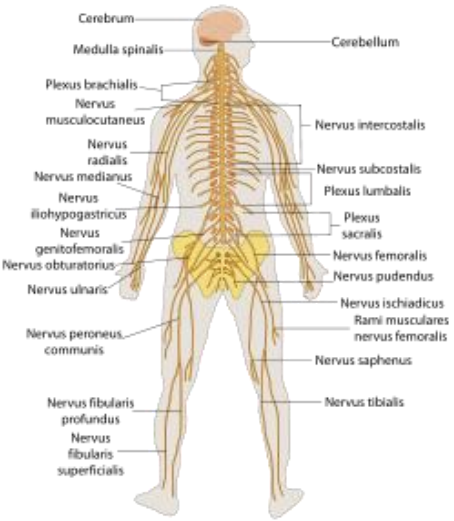


Figure 2.1 Human nervous system

At the cellular level, the cells that transmit the signals from the CNS to the rest of the body through the nerves are called neurons. The signals are transmitted by differences of potential in the neurons, which cause at the synapses (junctions between cells) the release of chemicals called neurotransmitters.

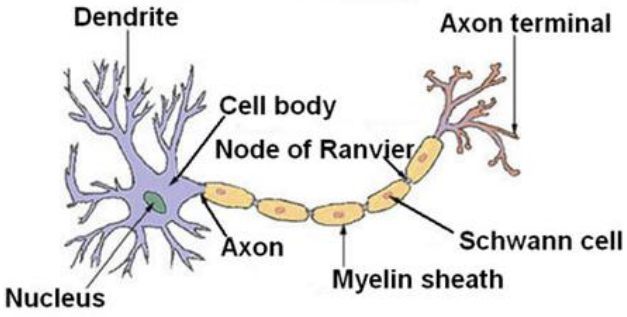


Figure 2.2 Parts of the neuron

The brain is the most important and bulky area of the nervous system. It is divided into two hemispheres (left and right) separated by the longitudinal fissure and communicated with the corpus callosum. The surface is what is called the cerebral cortex, formed by folds (gyrus) of grey matter, below which it is found the white matter. In deeper areas of the brain there are nucleus of grey matter, such as the thalamus, the caudate nucleus and the hypothalamus.

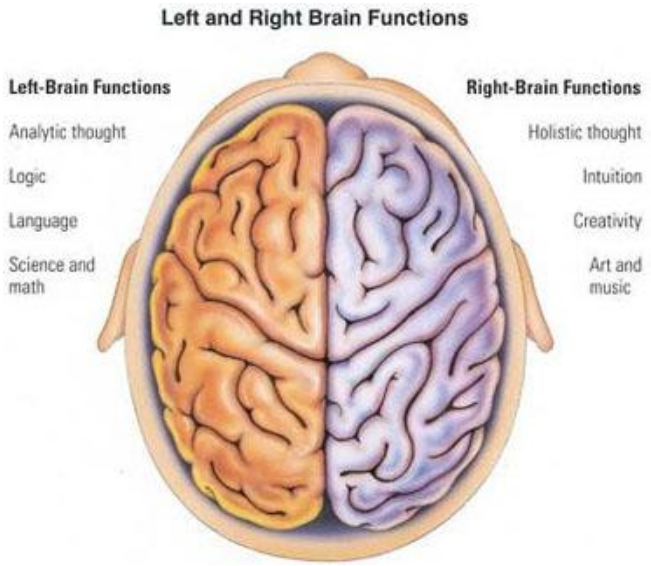


Figure 2.3 Brain hemispheres

Each cerebral hemisphere is divided in four lobes; frontal, parietal, temporal and occipital; separated by the central, parieto-occipital, lateral and calcarine sulcus. The frontal lobe is located in the anterior area of the central sulcus, above the lateral sulcus. The parietal lobe is located posterior to the central sulcus, over the lateral sulcus. The occipital lobe is located below the parieto-occipital sulcus. Finally, the temporal lobe is located below the lateral sulcus.

The frontal lobe is divided into six areas: the primary motor area, the pre-motor area, the supplementary motor area, the frontal ocular field, the Broca's area and the pre-frontal cortex. It mainly controls the motor functions of the body and the formation of words in the language (Broca's area). Moreover, the frontal lobe contains most of the dopamine-sensitive neurons in the cerebral cortex, associated with functions of reward, attention, short-term memory, planning and motivation.

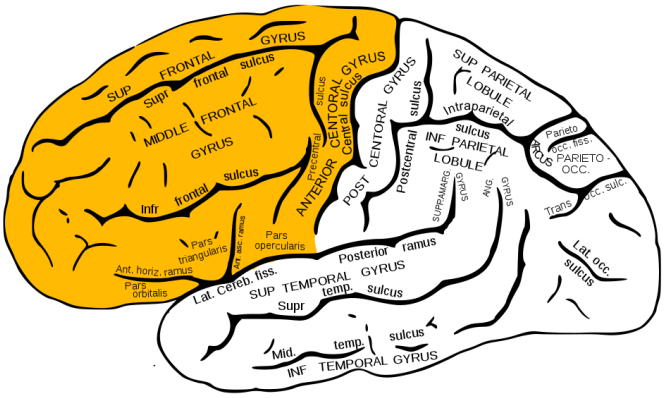


Figure 2.4 Frontal lobe

The parietal lobe is divided in the primary somatosensorial area and the association somatosensorial area. Its function is mainly that of integrating sensory information from different modalities, particularly determining spatial sense and navigation. It also includes the processing of the information related to the sense of touch and the visuospatial processing.

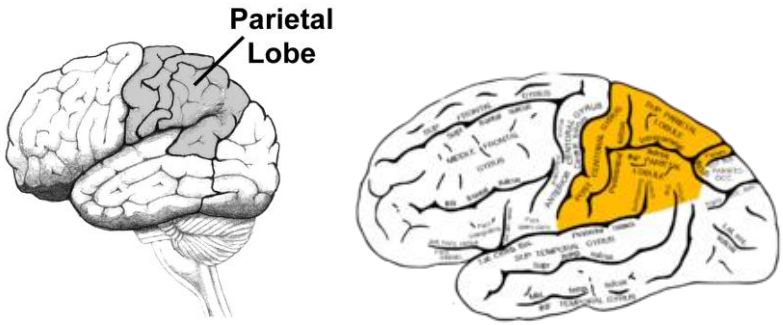


Figure 2.5 Parietal lobe

The occipital lobe contains the primary and secondary visual areas, related to the processing of the visual stimulus. The primary visual cortex is commonly called V1 or striate cortex, and the regions outside it called extrastriate cortex. Those extrastriate regions are specialized in different visual tasks, such as visuospatial processing, color discrimination and motion perception.

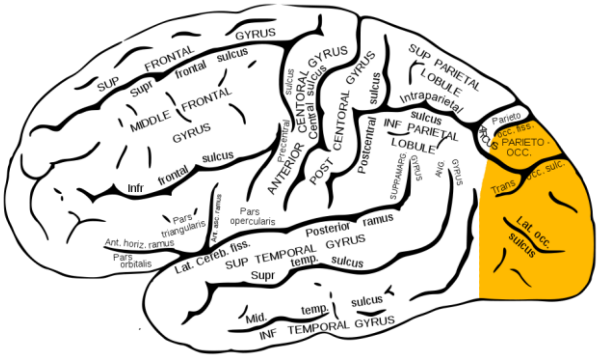


Figure 2.6 Occipital lobe

The temporal lobe consists in the primary and secondary auditory areas, and the Wernicke's area. Between its many functions, apart from the auditory processing, there can be mentioned retention of visual memories, processing sensory input, comprehending language (Wernicke's area, directly connected with the Broca's area in the frontal lobe by the arcuate fasciculus), storing new memories, emotion, and deriving meaning.

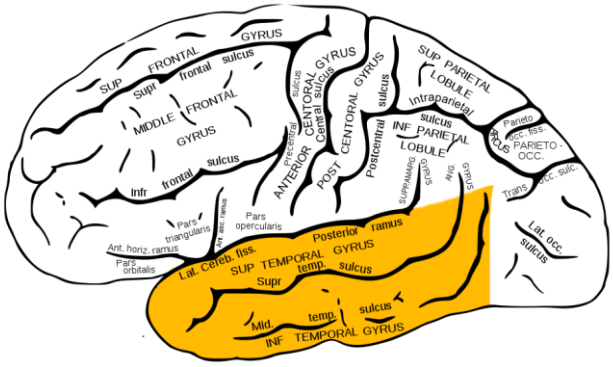


Figure 2.7 Temporal lobe

Apart from those four main lobes, the brain contains the limbic lobe and the insula. The limbic lobe is an arc-shaped region on the medial surface of each cerebral hemisphere, formed by parts of the frontal, parietal and temporal lobes. It is mainly formed by the cingulate and the parahippocampal gyri, and related to the sense of smell. However, more recently several studies have remarked the connection of the limbic lobe with emotion and behavior. The insula is an area of the cerebral cortex folded deep inside the lateral sulcus (in both hemispheres). It is believed to play a key role in consciousness and emotion and regulation of body's homeostasis. These functions include perception, motor control, self-awareness, cognitive functioning, and interpersonal experience.

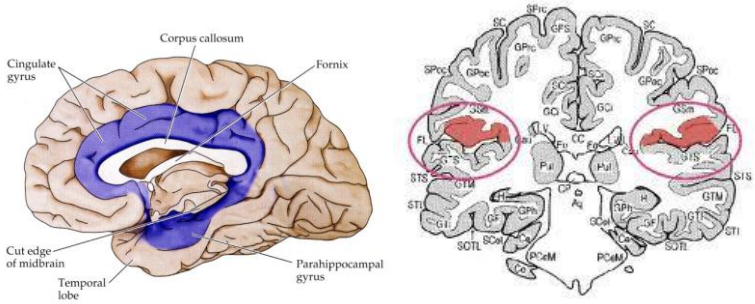


Figure 2.8 a) Limbic lobe, b) Insula

2.2 Introduction to Neuropsychotherapy

Traditional psychotherapy aims to treat the mental disorders following validated therapeutic processes based on the patient's individual life experiences. In words of LeDoux (2002, p. 299), "psychotherapy is fundamentally a learning process for its patients, and as such is a way to rewire the brain. In this sense, psychotherapy ultimately uses biological mechanisms to treat mental illness". According to this state, mental processes can be effectively and permanently altered through psychotherapy.

However, new courses of research are demonstrating that this traditional way of treating the disorder could be improved using the information available about the brain and its plasticity. As Klaus Grawe remarked in his book Neuropsychotherapy (Grawe, 2007), all mental processes are based on neural processes; so a better understanding of the brain function may help to the higher success of the psychological therapy.

It has been proved that psychotherapy, at the same time that it leads to behavioral change, achieves an effect through changes in the gene expression at the neuronal level (Kandel, 1996). Consequently, the success of a psychotherapeutic treatment relies on the structural changes in the neurons involved. From a neuroscientific point of view, the new neuroimaging methods could not only help in the diagnosis of mental illnesses, but also in the assurance of the effectiveness of psychotherapy (Kandel, 1996, p. 711). In words of Grawe (2007), "Such a neuroscientific explanation of already existing therapeutic strategies does not result in the creation of a new form of psychotherapy but instead yields a new perspective on psychotherapy".

Neuropsychotherapy is aimed to bring a new neuroscientific point of view to the problems that already exist over psychotherapy, helping to understand the mental disorder not only as a behavioral or emotional problem, but also as a change in the activation of the brain

areas involved in the illness and, consequently, in the neural connections that yield under them. Moreover, the neural system has demonstrated to present a high degree of plasticity, even during adulthood; so the brain continues to respond remarkably well to recurring stimulation of high intensity, retaining its ability to form new neural structures (Grawe, 2007). Psychotherapy could use this neural plasticity to design new courses of treatment based on new forms of stimulation, intense and frequent enough, to modulate the brain activations and change their functioning.

So according to the neuropsychotherapy theory, a better understanding of brain functioning could lead to a better treatment of several mental diseases, and there is where the new neuroimaging techniques appear as a fundamental tool to achieve those goals. In this Thesis, neuroimaging will be used for the study of changes in brain activations before and after undergoing a psychological treatment. This knowledge would lead to a future change in the therapy itself, adapting it in order to model the brain activations in the patient to make them closer to those considered normal.

2.3 Evaluation of the brain activity: Neuroimaging Techniques

Once understood the importance that a deep understanding of the functioning and structure of the brain has for neuropsychotherapy, the main characteristics of the two neuroimaging techniques applied for its study in this Thesis will be exposed: fMRI and EEG.

2.3.1 Introduction to the Magnetic Resonance

The main neuroimaging technique applied for the study in this Thesis is the functional magnetic resonance, an specific type of magnetic resonance which analyses the functioning of the brain based on its consume of oxygen in the active areas of the brain. In this section there will be done a detailed exposition of the historical evolution of this technique, its functioning and applications. Finally, it will be

explained how the analysis of the fMRI data in this Thesis was done, by means of a developed software: the SPM8 for Matlab.

2.3.1.1 Historical Introduction to the Magnetic Resonance

To study the origins of the magnetic resonance, it is needed to go back to the beginning of the 20th century, when in the early 30s Isidor Isaac Rabi analyzed the magnetic properties of the atoms. Rabi was a physicist at the Columbia University, who won the Nobel Prize in 1944 for his studies of the magnetic fields. He discovered that combining a magnetic field with radio waves he could make the nuclei of the atoms "flip", the property nowadays known as magnetic resonance. He founded the Molecular Beam Laboratory, where he collaborated with other scientists such as Sidney Millman, Jerrold Zacharias or Polykarp Kusch. The team attempted the use of an oscillating field instead of a steady one, which became the basis of the nuclear magnetic resonance method.

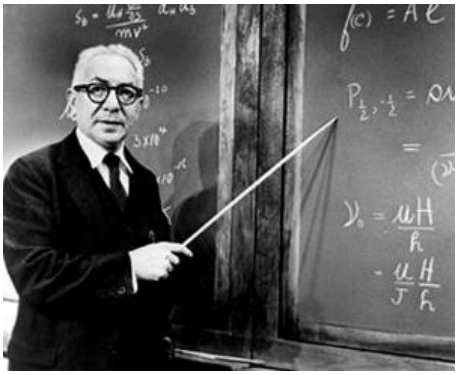


Figure 2.9 Isidor Isaac Rabi

But the idea of using this concept for the development of a new diagnosis technique was not formed until the 1970s, when two scientists individually (Paul Lauterbur from the State University of New York and Peter Mansfield from the University of Nottingham) originated the magnetic resonance imaging. Until then, the magnetic resonance had only been used for studying the chemical structure of substances, but the introduction of gradients in the magnetic field

allowed Lauterbur to determine the origin of the radio waves emitted from the nuclei, creating two-dimensional images of the body. Mansfield used this discovery and took it a step further, developing a mathematical process to speed the image reading. Mansfield is also credited with developing the MRI protocol called echo-planar imaging, which allows T2* weighted images to be collected many times faster than it was previously possible, making functional MRI feasible.

Figure 2.10 Paul Lauterbur (left) and Sir Peter Mansfield (right)

While Lauterbur and Mansfield focused on animals and human limbs, another American medical practitioner (Raymond V. Damadian) built the first full-body MRI machine, producing the first full MRI scan of the human body in 1977. Damadian discovered that tumors and normal tissue can be distinguish in vivo using NMR because of their relaxation times, and invented an apparatus and method to use it safely to scan the human body and diagnose cancer. This first attempt led to the creation of the first commercial MRI scanner in 1980.

Figure 2.11 a) Dr. Damadian explaining the function of the "live magnet" Indomitable in 1978, (b) Dr. Damadian years later posing with his prototype, c) Larry Minkoff testing the machine

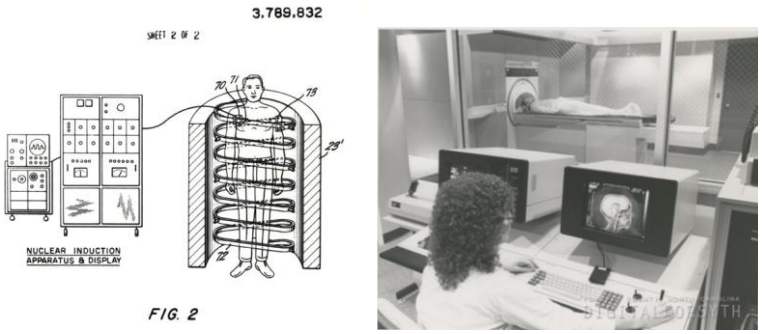


Figure 2.12 a) Prototype of the Indomitable included in the patent, (b) One of the first MRI commercial scanners (1983)

The next step came in the 1990s, when Seiji Ogawa, from the Bell Laboratories in New Jersey, found that oxygen-poor hemoglobin was affected differently by a magnetic field than oxygen-rich hemoglobin, which could be used to map images of the brain activity on a normal MRI scan. This properties of the hemoglobin were not new, as they has been studied back in the 1930s by Linus Pauling, who found that the magnetic properties of this blood cell depended on whether it had an oxygen molecule (being zero magnetic moment with oxygen, and sizeable magnetic moment without). The introduction of this concept in the magnetic resonance imaging method supposed the discovery of the functional MRI (fMRI).

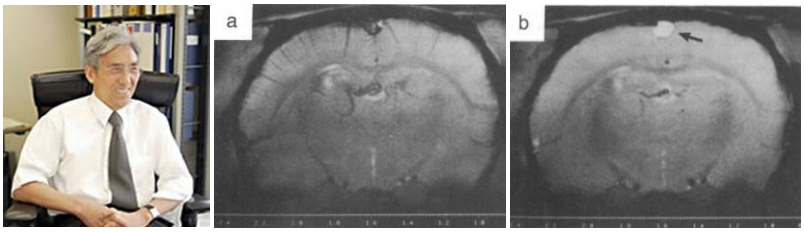


Figure 2.13 a) Seiji Ogawa, b) capture of some of the first MRI results with BOLD contrast, obtained by Ogawa et al. (1990)

The first attempt to apply this regional brain activity using MRI was performed by Jack W. Belliveau and colleagues (Harvard University) using a ferromagnetic contrast agent (Magnevist) (Rosen et al., 1991). However, this method is not popular in human fMRI because of the unsafe of the unnecessary injection and the short time the agent stays in the blood flow. In 1992, three studies were conducted to explore the BOLD contrast in humans. The first was performed by Kenneth K. Kwong and Jack W. Belliveau (between others) using gradient-echo EPI sequences at a magnetic field strength of 1.5T to study the brain activity related to the visual cortex (Kwong et al., 1992). In the second, Seiji Ogawa and colleagues used a 4T field to show that the BOLD signal depends on T2* loss of magnetization (Ogawa et al., 1992). The third study was conducted by Peter A. Bandettini (Bandettini et al., 1992), who used EPI at 1.5T to show the activation in the primary motor cortex, which controls voluntary movement.

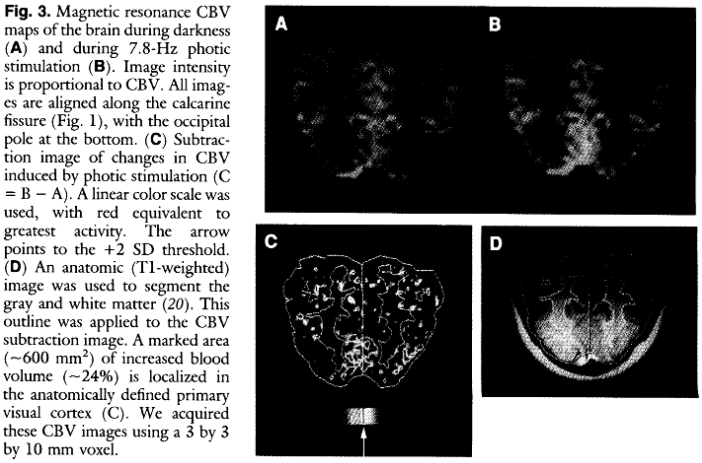


Fig. 3. Magnetic resonance CBV maps of the brain during darkness (**A**) and during 7.8-Hz photic stimulation (**B**). Image intensity is proportional to CBV. All images are aligned along the calcarine fissure (Fig. 1), with the occipital pole at the bottom. (**C**) Subtraction image of changes in CBV induced by photic stimulation (C = B − A). A linear color scale was used, with red equivalent to greatest activity. The arrow points to the +2 SD threshold. (**D**) An anatomic (T1-weighted) image was used to segment the gray and white matter (*20*). This outline was applied to the CBV subtraction image. A marked area (~600 mm^2) of increased blood volume (~24%) is localized in the anatomically defined primary visual cortex (C). We acquired these CBV images using a 3 by 3 by 10 mm voxel.

Figure 2.14 Capture of some of the results obtained by Belliveau et al. (1991)

2.3.1.2 Functioning of the Magnetic Resonance

Among the several brain image acquisition methods existing, the Magnetic Resonance is one of the most used due to the many advantages it presents when compared with other neuroimaging techniques. To begin with, it is a non invasive technique, which allows the measure of brain activation without any discomfort to the patient. Moreover, it has no secondary effects, so the experiments can be repeated several times without causing any damage to the subject. This allows, for example, the comparison between brain activations in different time moments (before and after passing a treatment, to put an example). This is because fMRI works in the range of no ionizing frequencies (10-100 MHz), which means the radiation it works with is harmless to people (unlike other image techniques such as Computed Tomography or X-rays).

But the main advantage of fMRI is the great spatial resolution it provides (between 1 and 3 mm), in comparison with other techniques such as EEG (Baumann et al., 2003). This makes the technique suitable to observe specific brain areas and neural networks that are activated during the task. It also presents a decent

temporal resolution (of the order of 1s for the whole volume of the brain) (Baumann et al., 2003).

Between the disadvantages, it should be mentioned the long exploration time it takes to have a complete scan of the brain. This, joined with the fact that the subject has to lay inside the machine and remain still all this time, makes the scan a bit uncomfortable to the subject (in some cases even provoking claustrophobia). Another disadvantage is the size and prize of the magnetic resonance scan, which reduces its use practically to hospital environments. Finally, metallic objects are not allowed inside the magnetic field, so the devices used inside the machinery have to be adapted for its use inside the fMRI.

Its way of operating is probably the most complex to understand among the medical image techniques. It is based in three physic principles: the phenomenon of polarization (the nucleus magnetization tends to equilibrium in order to align with an extern magnetic field of high intensity), precession (the magnetization, out of the equilibrium state caused by an extern magnetic pulse, precesses around an axis) and relaxation (the magnetization returns to the equilibrium state once the external pulse disappears).

To understand the polarization, first it has to be understood that any nucleus formed by an odd number of protons and/or neutrons has a spin (rotation around an axis) and an angular moment (amount of rotation movement). The rotation of an electric charge generates an electric current, which makes the spin behave as a magnetic dipole. Those dipoles, in absence of a magnetic field, are randomly orientated (Figure 2.1Figure 2.15(a)). When a constant magnetic field is applied (typical in MR of 1.5-3T), those spines align themselves with the parallel direction (minimum energy state) or the anti-parallel direction (maximum energy state) to this external magnetic field (that will be called B_0), due to the increase of external temperature (Figure 2.15(b)).

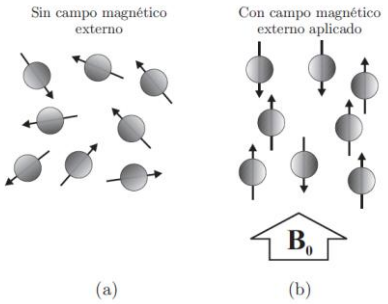


Figure 2.15 (a) In absence of an external magnetic field, the spins are randomly oriented. (b) When an external B_0 field is applied, every spin is aligned with the parallel or anti-parallel direction

The population in both states is more or less the same (100,000 spins of maximum energy and 100,006 of minimum energy, approximately), but this small difference provokes the existence of a net magnetization parallel to B_0 and null in the transversal direction. In reality, this alignment is not exactly parallel, but with certain degree of angulation, which makes the spin associated with the magnetic moment precess around an axis parallel to B_0 (Figure 2.16). Precession is the rotation movement of the spin's axis around another axis (the proton, besides rotating around its own axis, precesses around another axis). The speed of precession of those spins follows the formula:

$$\omega = \gamma B_0$$

Equation 2.1 Speed of precession of the spins

where ω is the angular precession frequency of M, γ is the gyromagnetic ratio and B_0 is the extern magnetic field intensity.

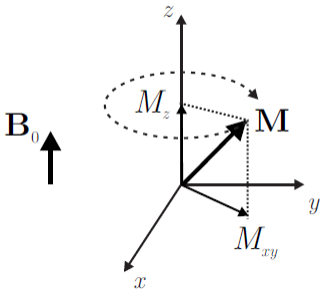


Figure 2.16 The magnetization vector precesses around the longitudinal axis, which is the one parallel to the external magnetic field

As the 60% of the human body is composed of water (H_2O) and the ^1H nucleus has a molar concentration much higher than the rest of the nuclei (99 mol/l) with a sensibility higher than the other elements, this nucleus will be the one used. For a magnetic field of 1.5T (typical in MR) and a gyromagnetic ratio for ^1H of 42.57 MHz/T, it gives an ω=63.85 MHz, known as the Larmor frequency (frequency of resonance for the nuclei).

When a new electromagnetic pulse B1 is emitted at the Larmor frequency, it will echo with the spines, moving them from their equilibrium position (those in the maximum energy state will change to the minimum energy state and vice versa until the populations of both states are equal), provoking in the resultant magnetization a precession effect around the longitudinal axis in which M follows a descent movement, resulting in a final magnetic moment null in the B_0 direction and maximum in the perpendicular direction (Figure 2.17).

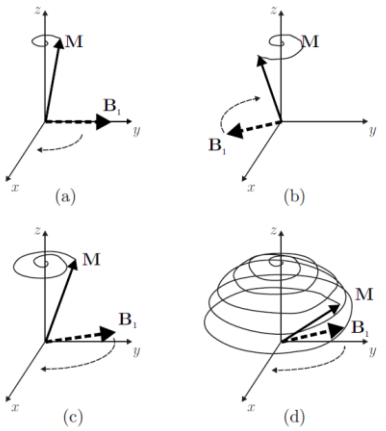


Figure 2.17 Phases of the precession process that the magnetization vector follows around the longitudinal axis

When the B_1 pulse ends, the next process begins, known as the relaxation; where the magnetic moment will return to its original equilibrium position. Then, the longitudinal magnetization will be maximum again (Figure 2.18(a)) due to the spin-medium interactions (T_1 decay); and the transversal magnetization will disappear (Figure 2.18(b)), due to the loss of energy caused by the spin-medium interaction and the local and random phase difference between the spins (T_2 decay). During this process some energy is emitted, which can be captured by several reels located on the perpendicular plane, where the magnetization induces an alternating current.

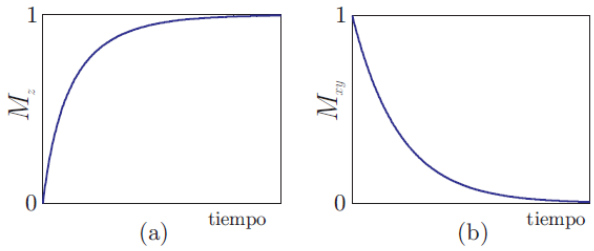


Figure 2.18 (a) Return of the longitudinal magnetization component M_z to its relax state according to T_1, (b) Transversal component M_{xy} decay to the null state according to T_2

2.3.1.3 Functioning of the Functional Magnetic Resonance

The functional magnetic resonance imaging (fMRI) technique is a relatively new method for using resonance images to measure the metabolic changes that occur in the active part of the brain. FMRI is more and more often the chosen method for the clinical diagnosis, allowing the study of the brain function; either it is a healthy, ill or damaged one; and helping in the evaluation of the existing risks in surgery and other treatments.

The brain areas that perform each function are more or less well known, but their exact location and function depends on each person. Moreover, the brain functions cannot be considered in isolation for each cortical area but there are several of them involved in each function (for example, when we heard something, in addition to the auditory area, other functions are active simultaneously: words interpretation, language formation to elaborate a response, phonetics…). Moreover, it has to be taken into account the effect of the vasodilatation in the arterial and venous vessels of the brain due to the higher oxygen consumption in the active areas, which produces a decrease in the amount of deoxyhemoglobin present, which has a magnetic effect (the hemoglobin molecule changes its magnetic proprieties depending on the union or no-union with the oxygen). That change in the oxygen concentration and the increase of dilatation is what it is measured inside the fMRI, being normally shown as a change in the color of the active areas over the gray background of the inactive areas.

This magnetization change in the hemoglobin is used to calculate the BOLD signal (Blood Oxygenation Level Dependant), which measures the oxyhemoglobin/deoxyhemoglobin rate in order to discern between the active and the inactive areas. If those images are taken in a rate of 1 or 2 images per second, the contrast between the active and inactive areas can be represented; obtaining the patient's cerebral map, functional and structural. More precisely, the blood that flows through the arteries comes from the heart and is

oxygenated, containing oxyhemoglobin (HbO_2), that produces a diamagnetic effect (repulsion to the magnetic field). However, the blood in the veins has already waste its oxygen feeding the active brain areas and contains deoxyhemoglobin (Hb), producing a paramagnetic signal (attraction to the magnetic field).

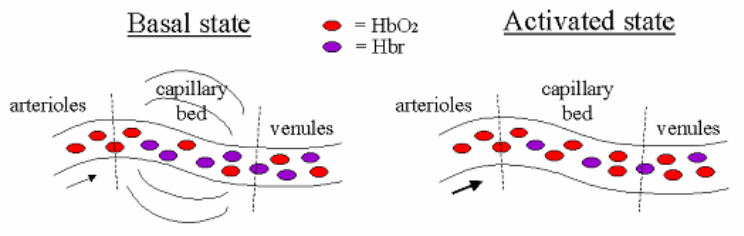


Figure 2.19 Oxyhemoglobin and deoxyhemoglobin concentrations in the capillary beds for the basal and activated states

To sum up, the process goes as follows: the increase in the neuronal activity provokes the freeing of vasoactive substances by the neurons, which causes the vascular dilatation and the corresponding increase in the blood flow. This compensates the increase of deoxyhemoglobin caused by the increase in activity that had consumed the oxygen reserves. The increase in the oxygenate blood flow "cleans" the deoxygenate one, increasing the level of oxyhemoglobin present. The magnetic resonance signal that had been suppressed by the deoxygenate hemoglobin increases now, which allows the measure of the BOLD signal. The maximum BOLD signal amplitude is measured between 4 and 6 seconds after the event, which slows down the process.

2.3.1.4 Capture of fMRI images

When in the edge to design a fMRI system, the interaction of four elements is needed to capture the image: a high intensity magnetic field B_0 in the longitudinal direction (produced by a superconductor electromagnet), several antennas to produce a transversal magnetic field that changes in time at the Larmor frequency (B_1), a group of reception antennas (also in the transversal direction) that could be the same used for emitting B_1, and three field gradients to produce

the spatial variation of the longitudinal magnetic field with respect to the three axis (G_x, G_y and G_z). Those gradients allow the caption of the image and its spatial differentiation.

The first of the gradients to be emitted is the G_z, which changes with the longitudinal direction, allowing the selection of the slice to represent. This gradient will change with the position in the z axis, which is translated in the selection of the axial slice at certain high. For each gradient G_z, it will be emitted a G_y gradient, which will make the precessing spins change their speed. When this gradient ends the image rows will spin again at the same speed, with the phase between them changed due to the time they spun at different speeds. This process is known as the phase code: each row of the image (y axis) will have a different phase, allowing the spatial differentiation in this axis. At last, it is made the frequency coding by the emission of a new gradient G_x, at the same time as the data are captured. The process is similar to the previous one: when the G_x gradient is emitted, each column of the image precesses at a different speed (which means with a different frequency, distinct to the Larmor frequency). That is translated in a spatial differentiation in x (columns) and y (rows) for each slice z. During this last gradient the data are captured, because once the G_x gradient ends all the columns will return to the Larmor frequency, as it happened with the rows when ending G_y. The graphic representation of those three gradients can be seen in the following figure (Figure 2.20):

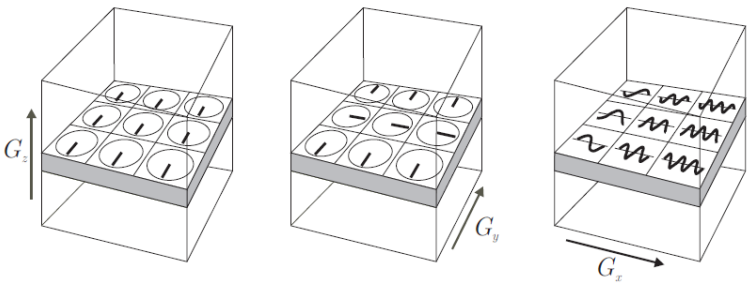


Figure 2.20 Visual description of the three gradients applied

This process is known as selective excitement: the greater the bandwidth of the radiofrequency field, the thinner the selected slice. In the same way, the more intensity or less bandwidth of the field gradient, the minor will be the slice's amplitude.

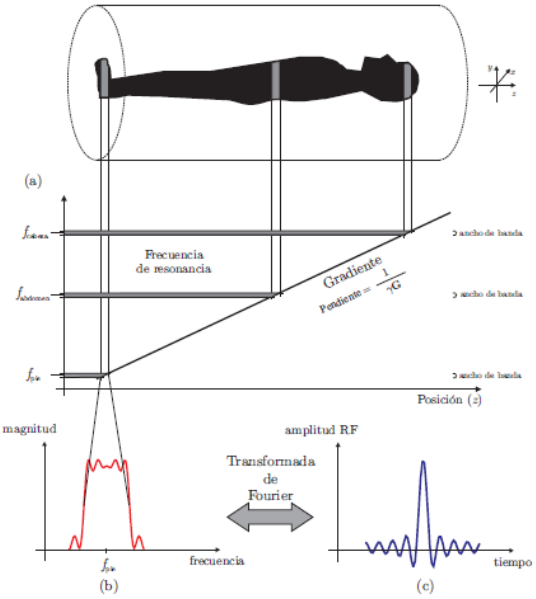


Figure 2.21 (a) G_z gradient for the excitement of certain slice, (b) frequency profile obtained, (c) RF pulse, Fourier transform of the frequency profile

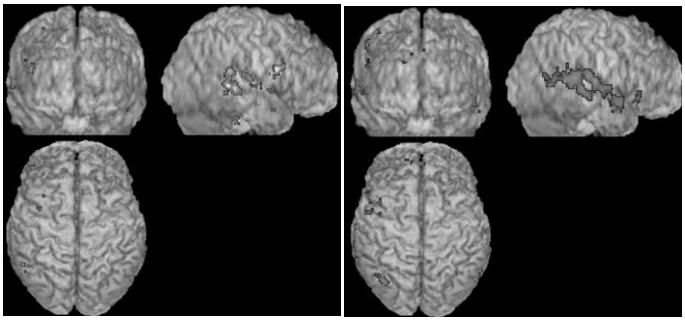
2.3.1.5 Applications of the fMRI

Several studies have been made in the fMRI field to analyze the activation maps obtained both in healthy and mentally ill people. A profound knowledge about the brain areas activated in each process can help in the understanding of some mental disorders and their precedence, and help to improve their treatment. For the fMRI measures, normally it is used the BOLD signal, which generates results more accurate of the brain areas active each moment.

Once the patient has been placed inside the magnetic resonance, some kind of stimulus has to be applied to provoke the activation of the brain areas of interest. Between the possible stimuli available,

the most used are the visual ones (using compatible MR glasses), the auditory (using compatible headphones), sensitive (for example, heat application for the measure of pain reaction)… Because the MR is a big magnet and the introduction of any kind of metallic object inside the MR room is forbidden, several companies are specialized in the fabrication of MR compatible devices to allow the presentation of stimuli inside the fMRI. Between the possible applications of this technique, there can be highlighted the study and treatment of mental disorders (psychosis, phobias, neurosis…), the study of pain distractors, the search of malfunctions in the brain…

Let's analyze some examples of researches done with fMRI. In a study conducted by Sanjuan et al. (2005), they applied auditory stimuli to psychotic patients, using words the subjects were used to hear in chains of 13 emotional words (4 negative imperative words, 3 insults, 2 imperatives, 2 emotional exclamations and 2 positive words) and 13 neutral words with a similar syntactic complexity. In this case, blocks of emotional and neutral words were alternated each 20s, for the avoidance of habituation, exhaustion, saturation or surprise. In 2007, the same group conducted a similar study, this time with schizophrenic patients, using as well auditory stimuli. The same methodology was used: alternated blocks of chains of words (20s each), first the neutral ones and then the emotional ones.



(a) (b)

Figure 2.22 Brain activations with neutral (a) and emotive (b) words, in the work of Sanjuan et al. (2005)

The fMRI techniques have also been applied for the study of emotions, which allows distinguishing between the brain areas activated for each kind of emotion. In a work developed by Canli et al. (2001) they analyzed women with two kinds of psychological behavior: some were extroverted women (optimistic people that enjoys the social treatment) and the other were neurotic (negative, anxious and apprehensive people). The shown stimuli were positive (couples, pets) and negative (guns, cemeteries) images, in 5 blocks of 4 images each. Those blocks were alternated, with duration of 7.5s/photograph. It was confirmed that the outgoing people showed greater activation in the cortical and subcortical areas, the cingulus and the amygdala when the positive stimuli were presented. On the other side, the neurotic people showed a greater activation in the left temporal lobe and frontal lobe for the negative stimuli. However, the outgoing people did not show any special activation for the negative stimuli, and vice versa. In the temporal cortex, it was proved the major reaction of the extroversion over the right hemisphere and of the neurosis over the left hemisphere. At last, they concluded that the negative images provoke a greater intensity of excitement than the positive ones. Women were used because they are supposed to show a greater emotional response, in comparison with the value judgments more typical of men. A study where they measured those differences was conducted by Lang et al. (1998), and they proved the greater activation in front of negative images than in front of positive ones over women, where men showed no difference. It was also measured the influence of the side where the stimuli were placed and its effect over the brain areas activated. Another study worth to mention is that of Ochner et al. (2002), who tried to modify the emotional response, voluntarily forcing a maintained, contained or strong emotional response; which allows regulating the brain activation.

VR has also been applied combined with fMRI for the study of active brain areas during the performance of certain tasks (Astur et al., 2005; Pine et al., 2002, Hoffman et al., 2003, 2004). This field of

study will be presented in more detail in the part of this Thesis about VR (section 2.4.2).

It is also worth to remark the part of fMRI studies related to the treatment of phobias, which is the aim of study of the second branch of research of this Thesis (Chapter 4). The phobia, and more precisely the spider's phobia, is characterized by the irrational fear of the sufferer to any contact with the feared animal.

Many experiments have been made about the treatment of spider's phobias with VR. Between the possibilities this technique provides, the most used are the visual stimuli, be those photographs (Dilger et al., 2003; Schienle et al., 2005; Straube et al., 2007; Wendt et al., 2008), videos (Paquette et al., 2003), immersive virtual environments (Baumann et al., 2003) or interpretation of words (Straube et al., 2004). All those studies and others with similar characteristics will be discussed in the corresponding chapter.

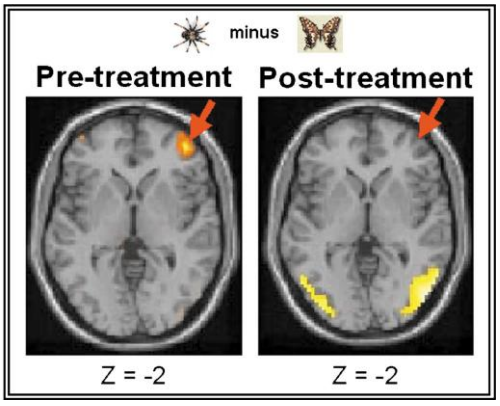


Figure 2.23 Example of brain activation results obtained studying phobic subjects (Paquette et al., 2003)

2.3.1.6 Analysis of the fMRI

The analysis of the fMRI images consists in three fundamental steps. First of all, the preprocessing of the data prepares the images (realigning and resizing them) to undergo the statistical analysis. Secondly, the data from each subject individually undergoes a first

level statistical analysis to obtain the comparisons between conditions. Finally, the data of all the subjects are compared in the second level analysis, to obtain the patterns of activation between subjects. In the following paragraphs these steps will be explained in more detail.

To analyze the fMRI data there are several programs available. In this Thesis, the one we used was the Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK), launched with Matlab Version 7.1 (MathWorks, Natick, Massachusetts, USA). The SPM is a program developed by Friston and Ashburner for Matlab, which allows the analysis of fMRI, PET, DTI and VBM images. As the developers describe it, "Statistical Parametric Mapping refers to the construction and assessment of spatially extended statistical processes used to test hypotheses about functional imaging data". Here the explanation will be centered in the analysis of fMRI images, allowing to measure the differences in brain activation due to the different tasks performed.

Before designing the protocol for the study, there are some issues to consider. First of all, it is important that the tasks to perform during the activation and rest periods were designed to be different only in the characteristics to measure, so the rest of the areas activated (visual, shape and word analysis, recognition…) are the same during both periods. For example, to analyze the brain activation due to the visualization of known shapes, during the rest period it should be performed the view of shapes without meaning. Doing so, the brain areas related to the visual area and the recognition of random shapes will be the same and only the areas related to recognition of known shapes will be activated.

Another issue to consider is which kind of design to develop. It can be a block design (long periods of alternating blocks of task and rest) or event-related design (measure the brain activation in the exact moment it occurs). In the block design, the brain activations are averaged, obtaining the mean activation for each block. In the event-

related design, there are considered the peak activations in each moment of time, taking into account that some actions have not an immediate brain response, but present a delay in the consequent activation.

Before using the SPM software, it is also important to avoid complex names in the fMRI data files, since they could cause failures in the program. There are two data formats allowed for fMRI images: Analyze and Nifti. SPM works with nifty, so if the images are given in another format they will have to be converted (for example, using the function dicom2nifti available in the website of SPM). Any complementary tool needed has to be copied in the “toolbox” folder of the SPM.

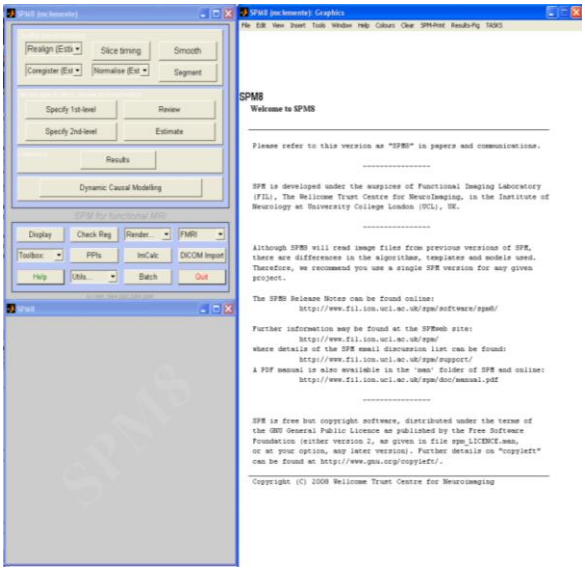


Figure 2.24 Capture of the SPM8

Before analyzing the fMRI data, the first scans captured should be excluded, in order to eliminate the decay of the fMRI signal associated with the moment when magnetization reaches equilibrium. Because of this, it is advisable to design the protocol beginning with a few black screen seconds. In the studies of this

Thesis, for example, this period consisted on 14s (or 7 scans), that is the time the device used lasted in reaching equilibrium. Then, the first step was to align the images to the AC-PC line (Figure 2.25). This line goes from the anterior to the posterior commissure of the brain. This step improves the convergence in the iterative processes.

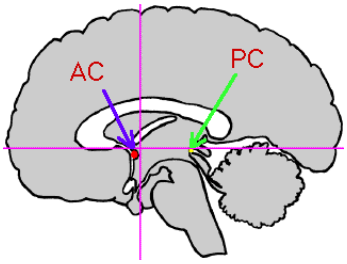


Figure 2.25 AC-PC line

The correct lateralization of the brain was also checked (the neurologic one, where the right side of the image is seen in the right part of the screen). Those two steps are conducted in SPM by opening the anatomical image using the option “Display” (Figure 2.26) and centering the origin of coordinates on the anterior commissure (AC), checking that the AC-PC line fits with the horizontal axis (Figure 2.27(a)). Once done the changes needed, to save them you have to copy the numbers indicated in the pointer position in mm in the right, forward and up fields that appear below in the window, changing their sign, and press “Reorient Images” (Figure 2.27(b)). To check if the orientation is correct, in the mm field the values have to be minor in the left than in the right part of the brain, and the opposite in the vx field.

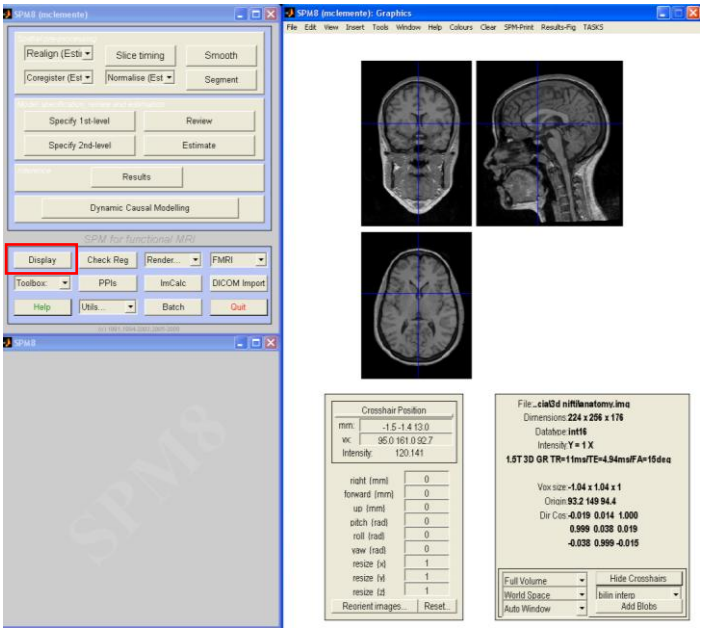


Figure 2.26 Capture of the Display option (showing the anatomic image)

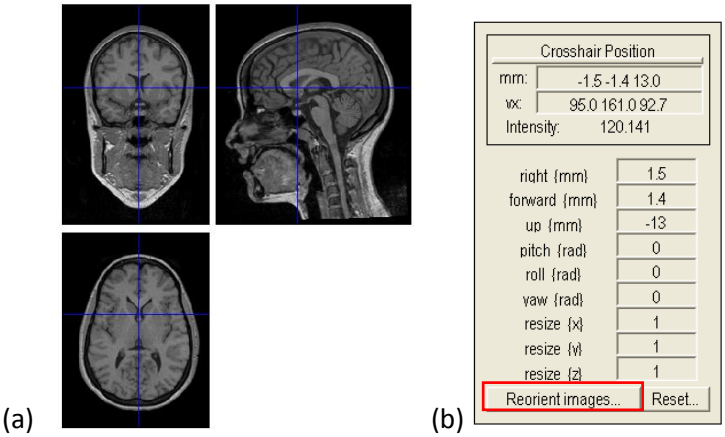


Figure 2.27 a) Capture of the anatomic image centered in the AC, with the horizontal axis crossing the AC-PC line, b) capture of the reorientation process to centre the anatomic image to the AC-PC line

Then the preprocess begins (Friston et al., 1995), which will consist in the realign of the images to the first scan, the coregistering of them to the structural one, the segmentation of the structural to obtain

the white matter, grey matter and cerebrospinal fluid images, the normalization of both the functional and the structural images and the smoothing with a Gaussian kernel. A schema of this process can be seen in the image below (Figure 2.28).

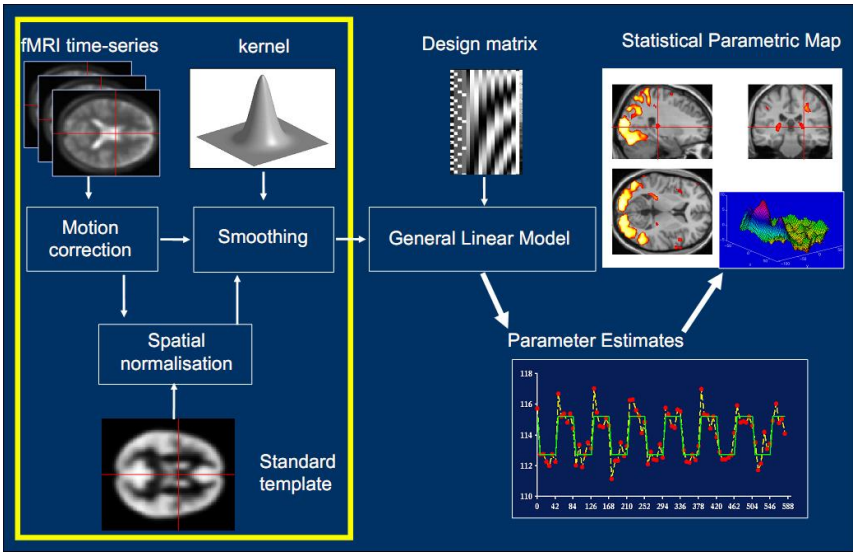


Figure 2.28 Schema of the steps followed in the SPM8 analysis. The yellow box marks the preprocess steps.

As aforementioned, the first step is the realignment of the functional images, which is achieved in SPM with the estimate and reslice option. This step resamples the images to rotate and translate them, in order to make them fit each other. In the case studied here, this option allows the correction of the movements the subject has committed during the scan, indicating when he has moved and if any data rejection is required. The option “Est & Res” (Figure 2.29), apart from estimating the register and saving it in the header of the image, creates a new registered image (renamed with the prefix r-). The most common option for the realignment is to do it towards the first scan, although it can also be made towards the most characteristic scan. In this study it was made towards the first scan. It should also be considered that movements greater than 2mm or 2^{o} should be rejected.

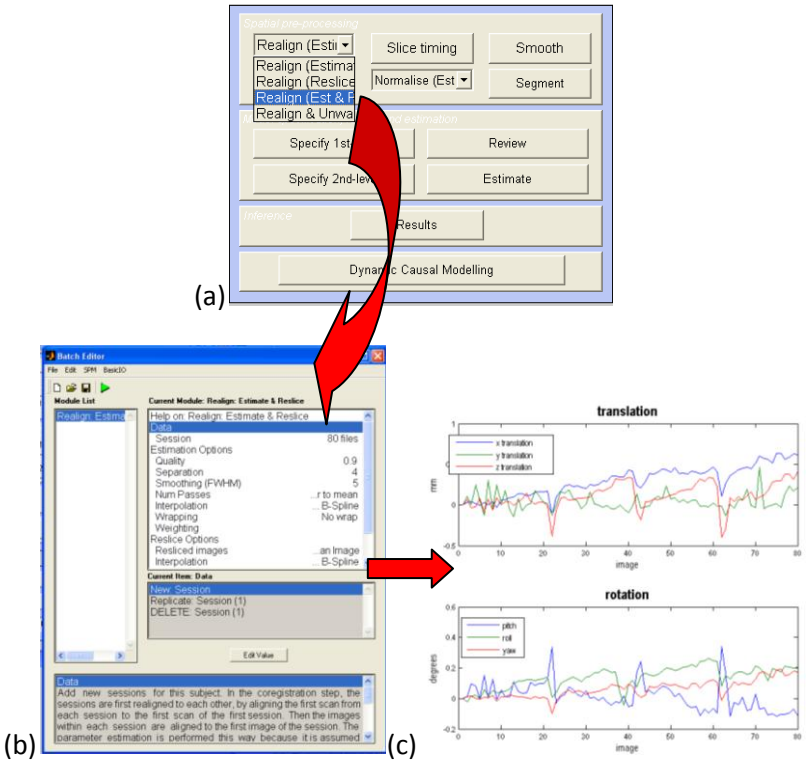


Figure 2.29 Captures of a) the SPM8 panel for the spatial pre-processing section, b) the batch editor for the "Realign (Est&Res)" option, and c) results of the translation and rotation corrections for each image

Once the functional images have been realigned, the next step is coregistering them to the structural images, using for this functions based on the Information Theory (entropy). The aim is to maximize what one image explains of the other (is is obtained a histogram of both images, showing the information about the levels of relationship between them). As a result, the corregistered images are obtained, saving the parameters in the header of the source image (Figure 2.30).

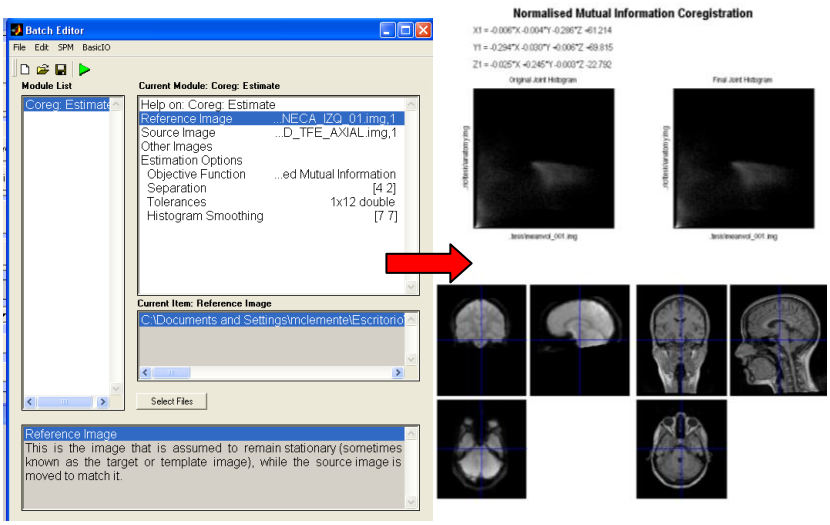


Figure 2.30 Capture of the batch editor for the "Coreg: Estimate" option and the results obtained

When the coregistering is done, the segmentation of the result ("Segment") is performed to obtain the gray matter, white matter and cerebrospinal fluid images (Figure 2.31 and Figure 2.32). Moreover, this step corrects the absence of uniformity in the intensity of the image (bias correction), to normalize it. Each of the images to segment corresponds to a different area of the histogram, selecting it by means of Gaussian filters, in order to be later normalized using the Discrete Cosine Transforms.

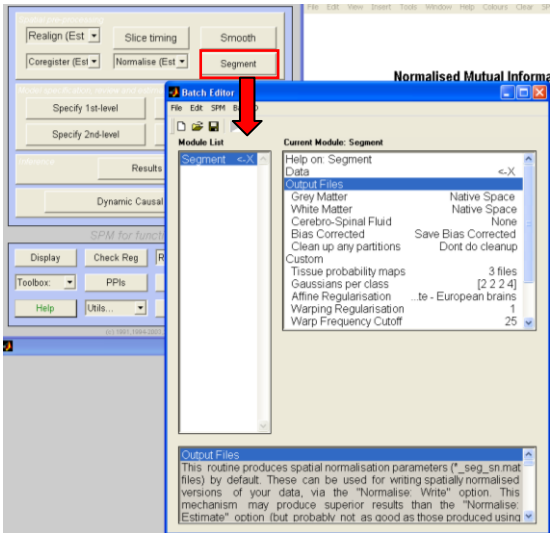


Figure 2.31 Capture of the Segment batch editor

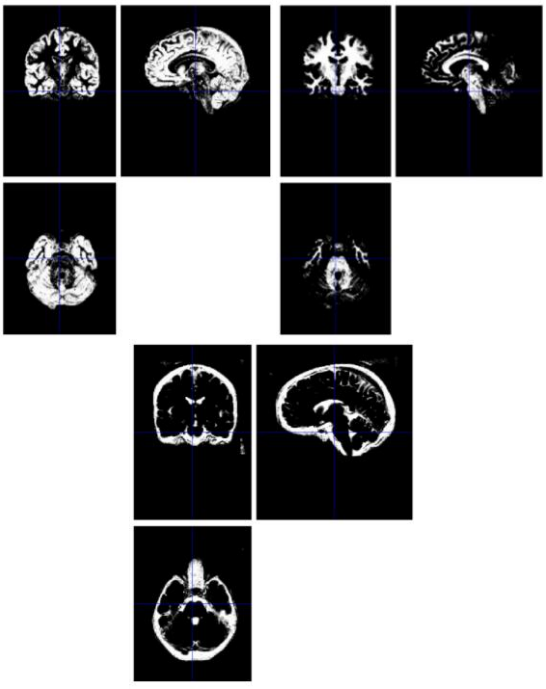
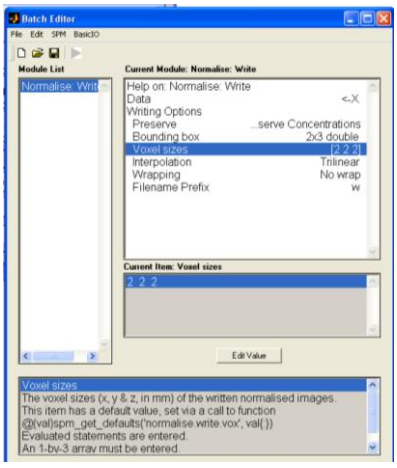


Figure 2.32 Captures of the a) Grey Matter, b) White Matter, and c) Cerebrospinal Fluid images

Then the normalization of the resliced functional volumes is made with the normalization parameters extracted after the segmentation and normalization of the anatomical volumes for each subject separately (template provided by the Montreal Neurological Institute). With this step it is obtained a between-subject register which allows the extrapolation of the findings obtained to a whole population, raise the statistical power and show the activations in coordinates of a reference brain (template). There exist two types of normalizations: based on tags (deforming the image until certain markers fit each other) or based on intensity (deforming to maximize a measure of likeliness between voxels). The aim is to obtain a low resolution image (blurred) which allows the average of the population. The normalization is made to a template of the same modality. First a related transform was made to adjust the position and size, and then a non-linear register to adjust the local differences (using Discrete Cosine Transforms). At last, a regularization is done to penalize the solutions that deform too much (more than 1.25). As a result, new images with the prefix w- are obtained for the structural as well as for the functional images, all of them situated in the standard stereotaxic space MNI (Figure 2.33).

(a) 

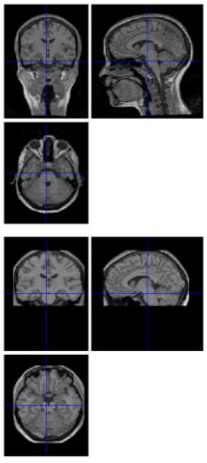
(b) 

Figure 2.33 a) Capture of the Normalization batch editor, b) comparison of the structural image before (top) and after (bottom) normalization

Finally, the smooth of the images is performed (Figure 2.34) using an isotropic Gaussian kernel or three-dimensional Gauss Bell (FWHM of 8 x 8 x 8 mm). This step erases the noise (high frequency, the shiny points in the image) to decrease the anatomic differences (images from different subjects are more similar when blurred). It also helps in the overlap, because the pixels that did not fit when mixed with their neighbors would be more similar (Figure 2.35). The full-width at half maximum (FWHM) of the Gaussian kernel is set to approximately the double of the voxel size. The filtering is made first in the horizontal direction and later in the vertical direction for mathematical efficiency.

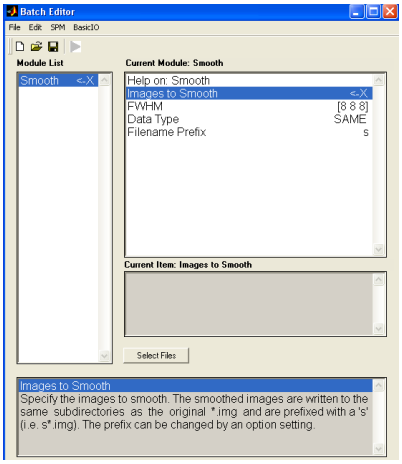


Figure 2.34 Caption of the Smooth batch editor

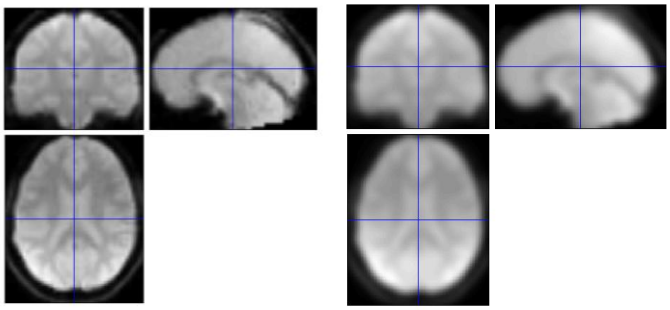


Figure 2.35 Comparison between a functional fMRI image before (left) and after (right) the smoothing

A capture of the SPM8 program for the preprocess block can be seen in the figure below (Figure 2.36).

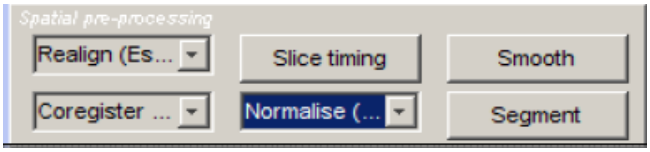


Figure 2.36 Capture of the preprocess group of the SPM8

Once the preprocessing has been made, the next step is to conduct a first level fixed-effect analysis (with the aim of detecting changes in the BOLD signal between conditions in a single subject), where the individual contrasts comparing between the different experimental conditions are obtained. For doing this, the hemodynamic response produced before any stimulus is used. In order to obtain it, the reconstruction of the whole brain volume each TR seconds (in the case studied here, each 2s) is made, composed of evenly spaced slices of TE seconds (Figure 2.37). That TE depends on the spatial resolution looked for: the greater the resolution, the longer the acquisition time and lower the signal to noise relation.

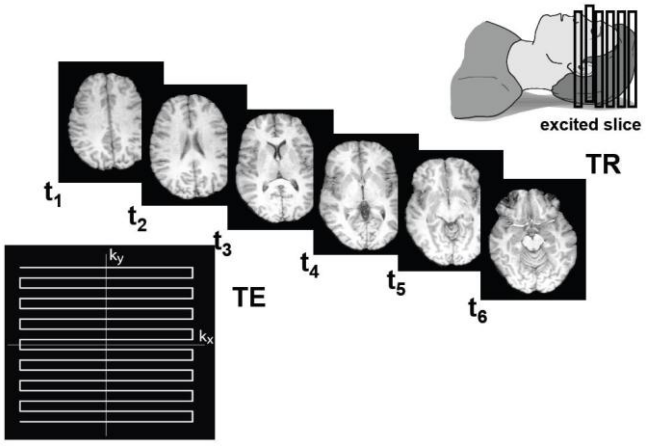


Figure 2.37 Relation between TR and TE

What it is understood as a first level analysis is to detect the changes in the BOLD signal between the different experimental conditions studied in an only subject. According to the general lineal model, the BOLD signal (which will be called Y) can be explained in the different time spots for each voxel, as the product of the design matrix (which will be called X) by the β parameters plus an error that measures the difference between the observed data and the data predicted by the model.

$$Y=X* \beta+ \varepsilon$$

Equation 2.2 Equation of the BOLD signal in terms of the design matrix

Where the design matrix contains the components which explain the observed data and β how much each component contributes to the value of Y. In practice, Y contains one column for each voxel with its gray levels through time, X contains the mathematic description of the experiment (a vector for each influential parameter, with value 0 if it is not activated and 1 if it is) and β are the regressors (one for each of the X components, which can be of interest – there is done statistic over them – or of non-interest – that explain what happened over the signal, for example, the head movements).

The first step was to construct the X matrix, pointing out all that happened during the experiment (design of the experimental model). In that way, there were estimated the β parameters to minimize the minimum square error.

$$\beta = (X^T * X)^{-1} * X^T * Y$$

Equation 2.3 Estimation of the β parameters

As a result, the X matrix appears as in the figure below (Figure 2.38), composed by the interest regressors (that were introduced in the design), followed by the base line (a column of ones to model the mean value or constant component, which SPM automatically includes) and the non-interest regressors (which normally contain the

movement corrections in rotation and translation, obtained during the preprocess).

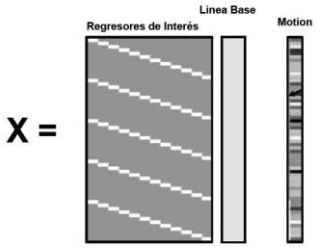


Figure 2.38 Design Matrix

As a result, the contrasts for the comparisons between conditions for each subject are obtained. It was also applied a high pass filter to eliminate the low frequency components in the signal caused by scanner motion and warming (at number of scans in a complete cycle*TR seconds). Once obtained the results for the first level analysis, there were estimated the model parameters (voxel-to-voxel analysis); that is, for each voxel it is studied if its temporal activation series fits the pattern specified by any of the regressors of the general lineal model.

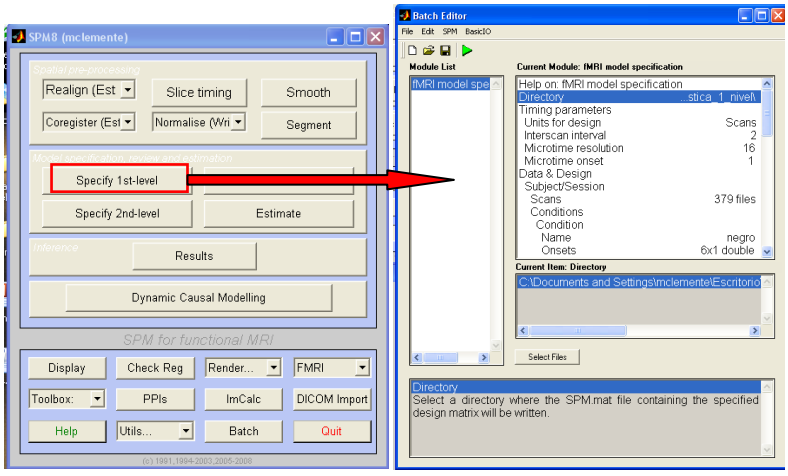


Figure 2.39 Caption of the first level analysis batch editor

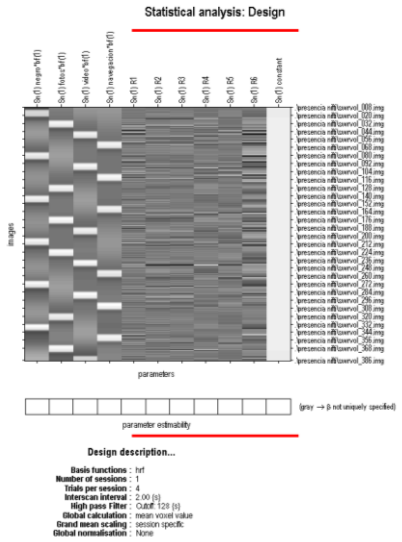


Figure 2.40 Caption of an example of a Design matrix

Group tests are performed at second level random effect analysis, where the group of subjects is taken into account. There can be distinguished two types of variables: the response ones or dependent (what it is measured, in this case the voxel intensity) and the predictor ones or independent (the factors used to measure the response). There exist, at the same time, two kinds of group analysis: fixed or FFX (only consider the intra-subject variability and work with preprocessed images) and the mixed or RFX (which take into account the variability intra- and between-subjects, and work with the con files generated in the first level analysis). In this work it was done a RFX study to compare all the subjects of the random effect sample (Figure 2.41).

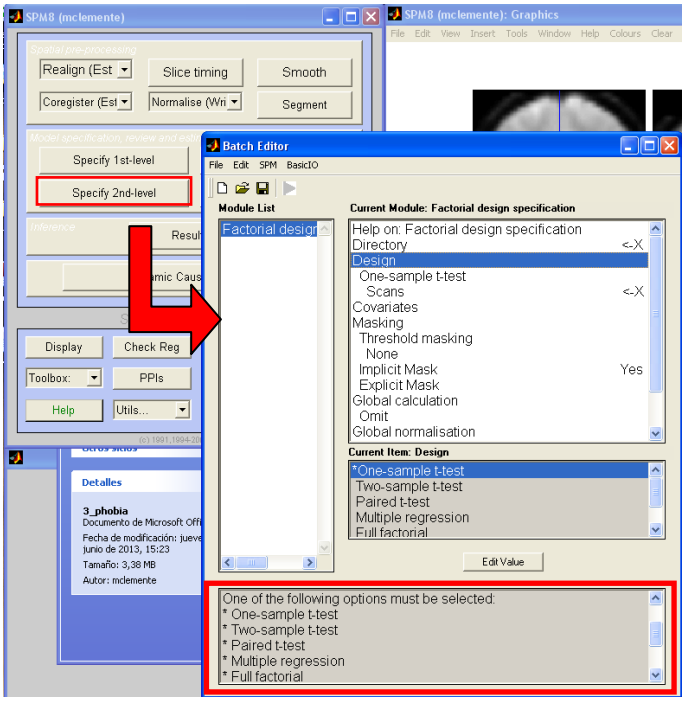


Figure 2.41 Caption of the second level analysis batch editor

Here is where the analysis changes depending on the study. In the sections describing each of the work lines there will be explained the analysis followed in more detail. Here, it will be just described the different second level analysis that can be performed:

- One Sample: analyze if in mean the activation level is significantly different of zero.
- Two Sample: study if the activation pattern is different between two independent populations (for example, between control subjects and patients).
- Paired Sample: study if the activation pattern is different between two related populations (for example, the same subject in different temporal moments).
- Multiple Regressions: allows the comparison between the activation pattern and some quantitative variable (for example, for including subjective test results passed after the scan and compare their results with the brain activations).

- Full factorial: to compare between the principal effects and the interactions from the ANOVA (for example, with three kinds of drugs, in different doses and over different populations).
- Flexible factorial: similar to the previous, but this one allows the selection of which principal effects and interactions are wanted to analyze.

Once chosen the second level analysis that better fits the specific design and introduced the parameters, the estimation of the results is obtained and begins the search for brain activations for each of the contrasts comparing the different experimental conditions. To obtain the specific brain areas that are activated in each contrast, it has been used the xjView (http://www.alivelearn.net/xjview8/) software utility for SPM that uses the MNI coordinates system (Figure 2.42).

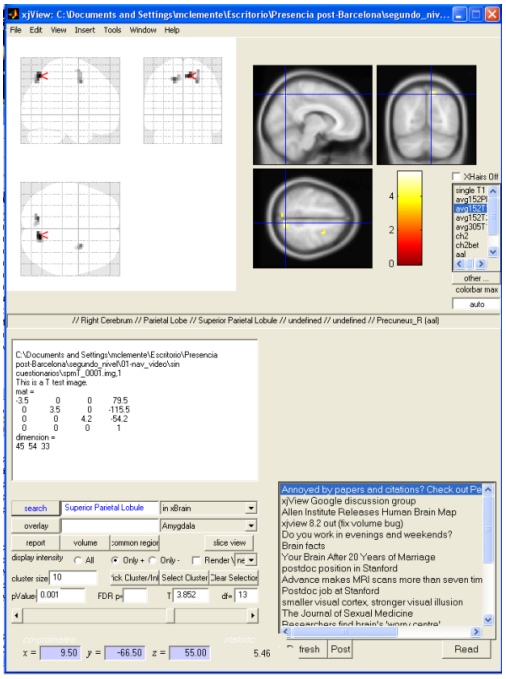


Figure 2.42 Capture of the xjView program

2.3.2 Introduction to EEG

The electroencephalography or EEG is a technique that measures the spontaneous electric activity of the brain along the scalp; more specifically, it measures the synaptic potentials resulting from ionic flows within the neurons in the cerebral cortex. EEG signals show the difference in potential between two electrodes, an active one and a reference one. It has been widely used, due to the freedom of movement it gives to the subject once the electrodes are placed. Moreover, the time resolution of the technique is of the order of milliseconds, allowing the measure of the fluctuations in the EEG signal due to the tasks developed. This level of time resolution is impossible to achieve with other neuroimaging techniques such as fMRI or CT. However, the spatial resolution is quite inferior to the one achieved with the later.

There are two techniques derived from the EEG: the EP (evoked potentials), and the ERP (event-related potentials). The EP averages the EEG activity time-locked to the presentation of a stimulus (may it be visual, somatosensory or auditory); while the ERP averages the EEG responses that are time-locked to more complex processing of the stimuli.

The applications of the EEG are very varied. In neurology, for example, it has been widely used for the diagnosis of epilepsy, because subjects with this illness present abnormalities in their brain activity. It also helps in the diagnosis of coma, encephalopathies and brain death. It helps in the study of brain tumors and strokes, as well as other brain disorders. Finally, in the study of sleep and sleep disorders EEG is used to measure the brain activity during the different states of sleep in all night studies.

In the research field of presence, EEG has also been used. For example, Baumgartner et al. (2006) evaluated the cerebral activity related to the sense of presence using a multichannel EEG, applying the low-resolution brain electromagnetic tomography (LORETA) method to study the cortical structures that produce the neurophysiologic activation.

EEG has also been combined with virtual reality for different purposes. For example, Bayliss and Ballard (2000) used the EEG signals as brain-computer interface for the manipulation of a simple VR task. In another work, Lin et al. (2007) assessed the cognitive responses in drivers while undergoing a traffic-light's experiment inside a virtual reality dynamic driving environment, using EEG.

Now the EEG technique will be analyzed in more detail, describing its functioning, historical development and main characteristics.

2.3.2.1 Historical evolution of the EEG

The first human EEG data were collected by Hans Berger in 1924. However, several previous events lead to this achievement. In 1875, Richard Caton published his results about electrical phenomena of the exposed cerebral hemispheres of rabbits and monkeys. This discovery was crucial, revealing the electrical nature of the brain. Years later, in 1890, Adolf Beck published his investigations over the spontaneous electrical activity of the brain, conducted over rabbits and dogs.

The first animal EEG was performed by physiologist Vladimir Vladimirovich Pravdich-Neminsky in 1912. However, as aforementioned, the first human EEG recording was not performed until 1924 by Hans Berger. In fact, Berger was who invented the electroencephalogram and gave the device its name. He continued with his investigations about brain electric activity, especially interested in the alpha wave (neural oscillations in the frequency range of 8–12 Hz arising from synchronous and coherent electrical activity of thalamic pacemaker cells in humans) which he published in 1931. He was especially interested in the "alpha blockage", the process by which alpha waves decrease and beta waves increase upon a subject opening their eyes. This distinction earned the alpha wave the alternate title of "Berger's Wave".

The 1930s lead to several investigations about possible clinical uses of the EEG, mostly related to epilepsy. The epileptic abnormalities in

the brain electric waves were first studied by Fisher and Lowenback in 1934. Also in the 1930s, Franklin Offner incorporated the inkwriter to the EEG device. The first sleep studies did not arrive until 1953.

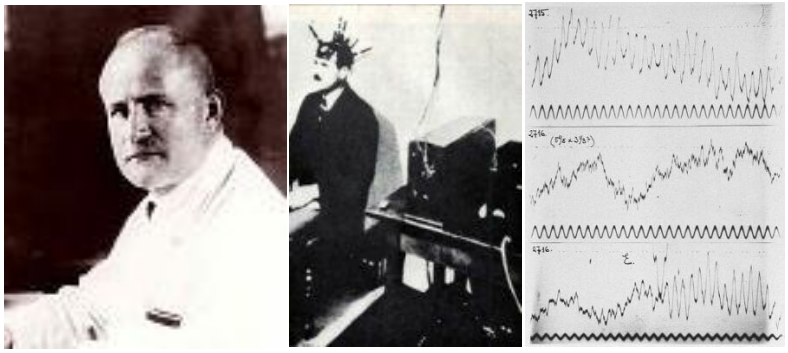
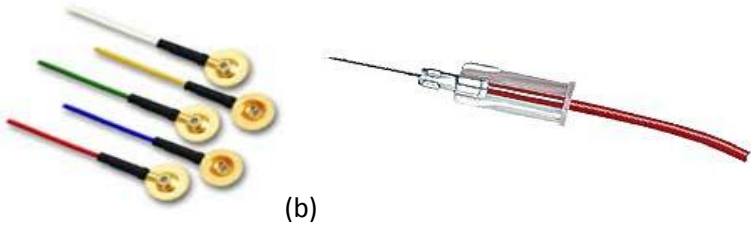


Figure 2.43 a) Hans Berger, b) One of Berger's patients and c) Recordings of EEG made by Berger

2.3.2.2 Functioning of EEG

The nervous system captures all the signals that arrive from the senses (external) and the organs (internal) and transmits them to the brain for its processing. It is done by means of the neurons. A neurotransmitter is a molecule in transition state, with a deficit or an excess of charge. It is transmitted through the myelin, which is the responsible of the neuronal synapses. Although the synapse is of a chemical nature, it has collateral electric effects, which is what is measured in EEG. The measurement can be done "in situ" with needle electrodes or in the scalp with superficial electrodes, less accurate but also less invasive. In the case of the EEG the superficial electrodes are the most commonly used.



(a) (b)

Figure 2.44 a) Surface electrodes, b) needle electrodes

An electroencephalogram consists of the electrodes, a pre-treatment block with an amplifier, a band pass filter and a receptor of the signal. The electrodes are re-covered with gold or silver and need of a conductor gel to improve the interface. The pre-treatment consists of a high input impedance, a high Common Mode Rejection Ratio and a low noise. The band pass filter restrains the signal between 0.5 and 100 Hz.

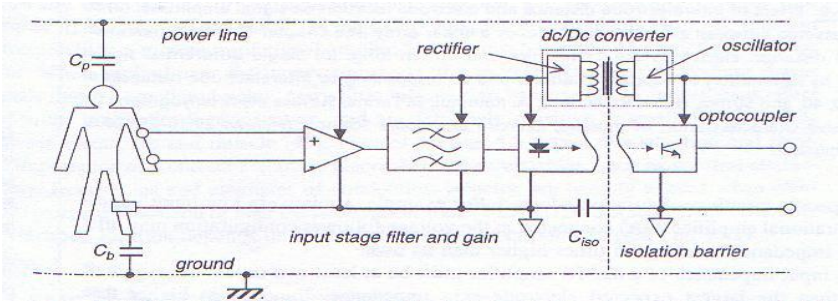


Figure 2.45 Schema of the system

The location of each electrode in the brain is fundamental, since the amplitude, phase and frequency of the signal will depend on it. For determining each position, first four key points of the head must be located: the nasion (between the eyes, over the nose), the inion (just opposite to the last, where the skull ends), and the pre-auricular points (left and right). Once measured the distance nasion-inion, there are marked the positions at 10%, 20%, 20%, 20%, 20%, 10% (as can be seen in the first picture below, Figure 2.46 left). The middle point of both distances nasion-inion and pre-auricular left-right is the vertex Cz (Figure 2.46, right). Apart from the signal electrodes, it is needed a ground electrode to work as reference.

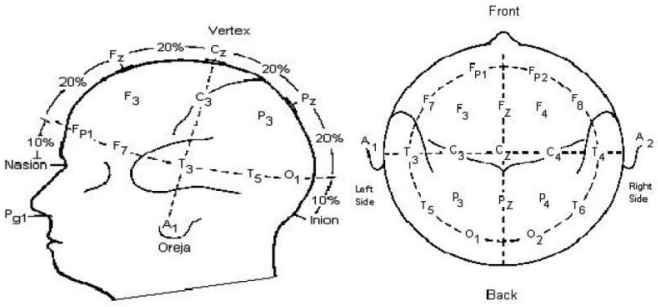


Figure 2.46 Location of the Nasion and Inion in the head (left), and location of the electrodes, with Cz in the center position (right)

Regarding the frequency spectrum, it can be divided in 6 bands:

- Alpha band: covers from 8-13 Hz and has normally an amplitude between 20-60 µV, although 100-200 µV are still considered normal.
- Beta band: above 13 Hz, normally between 18-25 Hz. The common amplitude is of 5-10 µV, almost never exceeding 30 µV. It comprises the fast waves.
- Theta band: between 4-7.5 Hz, and of low amplitude.
- Delta band: below 3.5 Hz. The theta and delta bands are considered the slow waves.
- Mu band: also known as alphoid because is contained also in 7-12 Hz (normally 8-10 Hz), with amplitudes between 20-60 µV. It consists in trains of few seconds of duration.
- Gamma band: is a pattern of neural oscillation in humans with a frequency between 25 and 100 Hz (typically 40 Hz). Gamma waves may be implicated in creating the unity of conscious perception.
- Lambda band: between 60 and 120 Hz, is a band contained in the occipital area of the scalp, related with the visual activity.

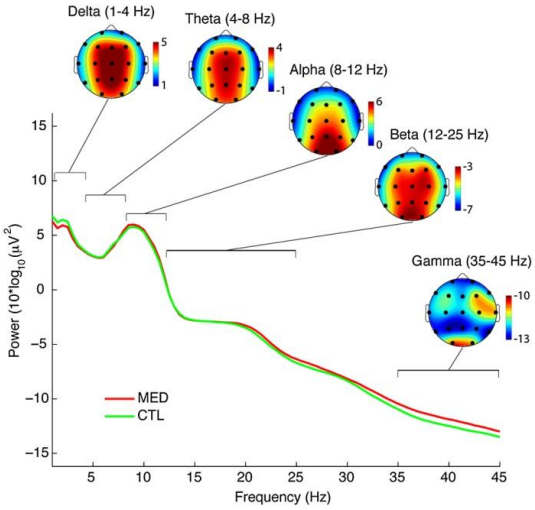


Figure 2.47 Power spectrum of the EEG

Once described the frequency bands, we will now analyze the rhythms associated to them that appear in the temporal EEG signal:

- Alpha Rhythm: is the most dominant rhythm in a normal EEG, mostly located symmetrically in the occipital and parietal areas (being especially evident while in relax with closed eyes).

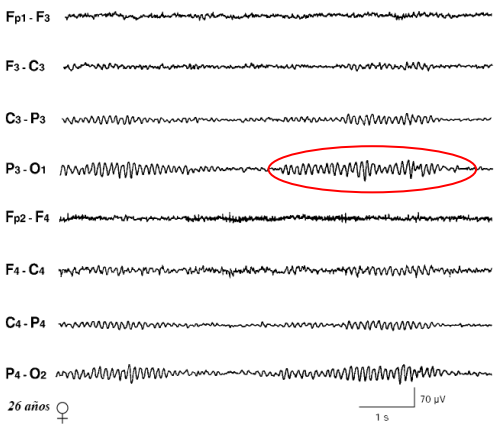


Figure 2.48 Alpha Rhythm in the posterior areas of the brain, remarked in red the period with the eyes closed

- Beta Rhythm: appears in nearly 20% of the healthy people, being thought that its significance is related to the sensorimotor function.

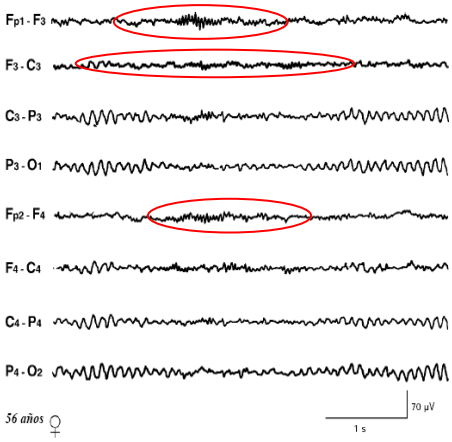


Figure 2.49 Beta Rhythm

- Mu Rhythm: is the less frequent to find, being in just the 10% of the healthy subjects. Mainly located in central areas, is recognizable for its morphology in arch shape. It is related (contralaterally) to the motor and sensorial systems.

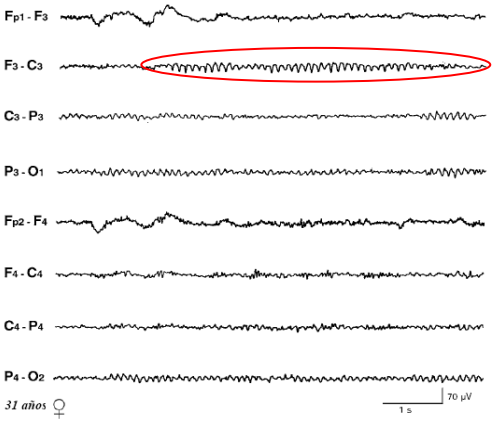


Figure 2.50 Mu Rhythm

- Lambda Rhythm: they are triangular, normally biphasic, sharp waves; 100-250 ms long and with low amplitude (less than 50 µV). They appear in occipital areas of the scalp and are related to the search movement of the eyes (that is why they are preceded by a potential in the frontal areas due to the eye movement).

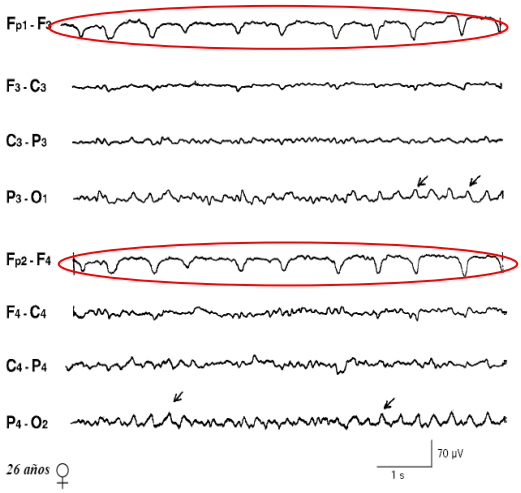


Figure 2.51 Lambda Rhythm in posterior areas while blinking

2.3.2.3 Advantages and disadvantages of the EEG

When comparing the EEG with other neuroimaging techniques, such as the fMRI presented before, it presents several advantages:

- Freedom of movement: in other neuroimaging techniques, such as fMRI or PET, the subject has to lay still, with the head's movement restrained by a special helmet, and trying to move any part of the body as little as possible. However, the EEG gives the subject more freedom in its movements and position, allowing him to remain sit or even stand. Although the movements are still restrained, a little more of movement is allowed. This makes the experience more natural to the user, so the brain activations are more specific to the task. Moreover, there are portable devices which allow measuring EEG in any location you want and in any position.

- High time resolution: the time resolution of the EEG is of the order of milliseconds, far better than those of other neuroimaging techniques (such as fMRI). This makes possible the continuous control of the electrical activity in the brain over time.
- Cheap: another important advantage of the technique is the prize, that is lower than most of the other neuroimaging techniques (far lower than fMRI, for example). Moreover, in the market there can be found several low-cost devices that allow to measure low-resolution EEG and which have a price that does not exceed the 200 €.
- Non-invasive to the patient: as well as in fMRI, EEG has no secondary effects over the subject and is non-invasive; which allows, between other things, the repetition of the scan (for example for pre-post treatment studies).

Despite the advantages of the EEG, there must be also pointed out some disadvantages. The most important is the bad spatial resolution this technique presents, compared to others such as fMRI. It is due to the fact that electric signals are measured through the scalp. If using needle electrodes, this disadvantage decreases, but it cannot be applied in non-clinical subjects. Moreover, the spatial resolution depends on the number of electrodes placed over the scalp (the more electrodes are placed, the better the spatial resolution acquired will be). The other big disadvantage is that the technique measures cortical activations, not being reliable in more internal areas of the brain. However, there are several tools (such as the sLORETA) which process the signals obtained from the EEG and approximate with good precision the brain activations in the internal areas.

2.3.2.4 EEG Devices

There are different kinds of EEG devices, from the classical clinical electroencephalogram to the new designed-for-games wireless headsets. For this study, it has been employed a cheap wireless portable device (the Emotiv EPOC). Now its main characteristics will be discussed.

The Emotiv EPOC is a design-for-games device, which means it is originally conceived for detecting player thoughts and feelings and used them to control the game. However, its usefulness in the research field has been already proven, and many studies are using it for EEG measures (Campbell et al., 2010; Khushaba et al., 2012, 2013). The Emotiv EPOC is a multichannel wireless portable headset, which has 14 data-collecting electrodes and 2 reference ones. It transmits the EEG data wirelessly to the computer. In the following table (Table 2.1) there are displayed some of the characteristics of this device.

Number of channels	14 data collecting and 2 reference ones (CMS and DRL)
Channel names (Int. 10-20 locations)	AF3, AF4, F3, F4, F7, F8, FC5, FC6, P3 (CMS), P4 (DRL), P7, P8, T7, T8, O1, O2
Sampling method	Sequential sampling, Single ADC
Sampling rate	~128Hz (2048Hz internal)
Resolution	16 bits (14 bits effective) 1 LSB = 0.51μV
Bandwidth	0.2 - 45Hz, digital notch filters at 50Hz and 60Hz
Dynamic range (input referred)	256mVpp
Coupling mode	AC coupled
Connectivity	Proprietary wireless, 2.4GHz band
Battery type	Li-poly
Battery life (typical)	12 hrs
Impedance measurement	Contact quality using patented system

Table 2.1 Characteristics of the Emotiv EPOC headset

Figure 2.52 Image of the Emotiv EPOC

Recently, several studies have been developed using the Emotiv EPOC headset, trying to demonstrate its usefulness and practical applications. Given its portability and its low-cost in comparison with other EEG devices, it is widely being used (especially in BCI applications) due to its high temporal resolution compared to other non-invasive techniques such as MEG, fMRI or the traditional EEG (Duvinage et al., 2012). For example, Campbell et al. (2010) used it as an interface to communicate the brain with a mobile phone application, in order to command it just with mental orders. More precisely a sequence of photos of contacts appears in the phone and when the showed photo matches that of the contact the user wants to dial, a P300 brain potential is elicited. In another study, Khushaba et al. (2012) explored the brain activations elicited while performing a task where decision making is involved. They used an Emotiv EPOC headset to measure the brain activity, as well as a Tobii-Studio eye tracker system to capture the participants' choice based on their preference in looking at. In a posterior study, the same group (Khushaba et al., 2013) explored the commercial applications of this decision making measures for the guidance to choose the marketing that better fits the consumer preferences. In this concrete study, they used again the Emotiv EPOC headset to measure brain activity while performing a choice task to choose among the user's preferred shape, flavor and topping in biscuits.

In the field of emotional induction, Rodríguez et al. (2013a) used virtual environments to provoke a negative mood (sadness) in the subjects. They measured the brain activation changes before and after the negative induction by means of an Emotiv EPOC headset. They also validated the use of this low-cost EEG device (Rodríguez et al., 2013b), by monitoring brain activity during a positive emotional induction (view of validated images from the IAPS system).

2.3.2.5 Analysis of EEG

The first step in the analysis of EEG is the preprocessing of the signals, which can be made by means of the EEGLAB program (Delorme and Makeig, 2004), launched with Matlab Version 7.1 (MathWorks, Natick, Massachusetts, USA). First, the data from EDF have to be imported and the data wanted from the sensors selected.

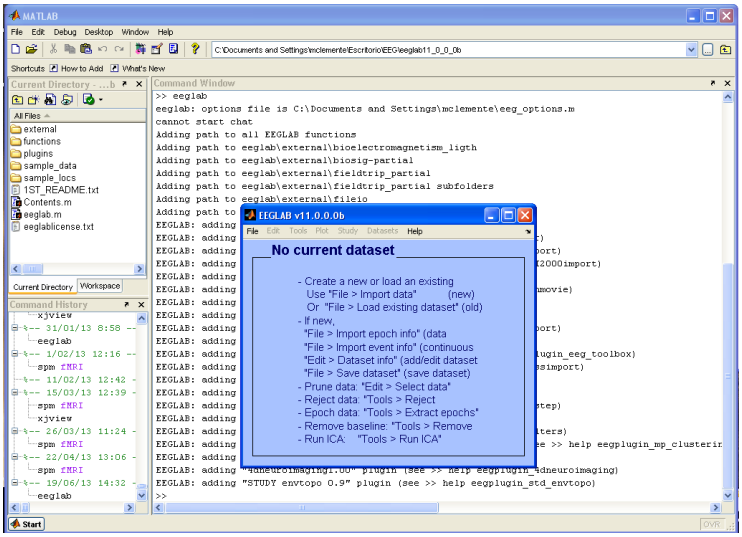
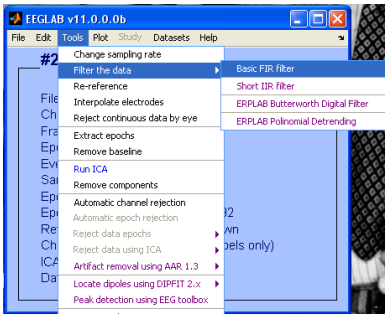


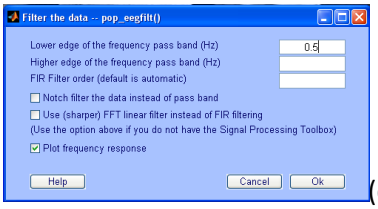
Figure 2.53 Capture of the EEGLAB launched with Matlab

Then, the baseline is removed and all the recorded EEG epochs have to be checked for artifacts. First of all, data have to be digitally filtered using a linear FIR band pass filter (0.5-45 Hz). This step is performed in two steps: first a high pass filter at 0.5Hz and then a low pass filter at 45Hz.

(a)



(b)



(c)

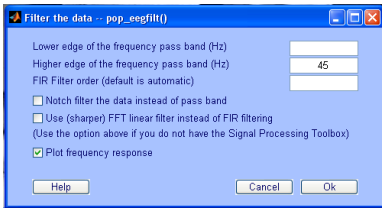
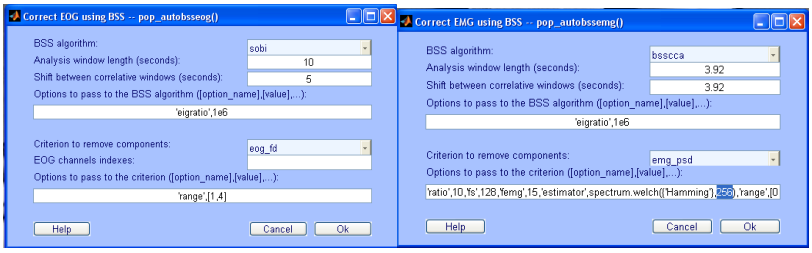


Figure 2.54 (a) Filter of the data with a basic FIR filter, (b) first the high pass filter at 0.5Hz and then (c) the low pass filter at 45Hz

Then, the electrooculographic (EOG) artifacts are removed by the application of the Blind Source Separation (BSS) method, using a window length of 10s, with 5s between windows. The electromyographic (EMG) artifacts are removed using also the BSS method.



(a) (b)

Figure 2.55 Correction of the (a) EOG and (b) EMG artifacts using BSS

For the analysis of the activated brain areas, the sLORETA (standardized low-resolution electromagnetic tomography) tool is used (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994, 1999; Frei

et al., 2001). The whole brain is analyzed using voxel-wise t-tests for examining the conditions of interest for the six frequency bands.

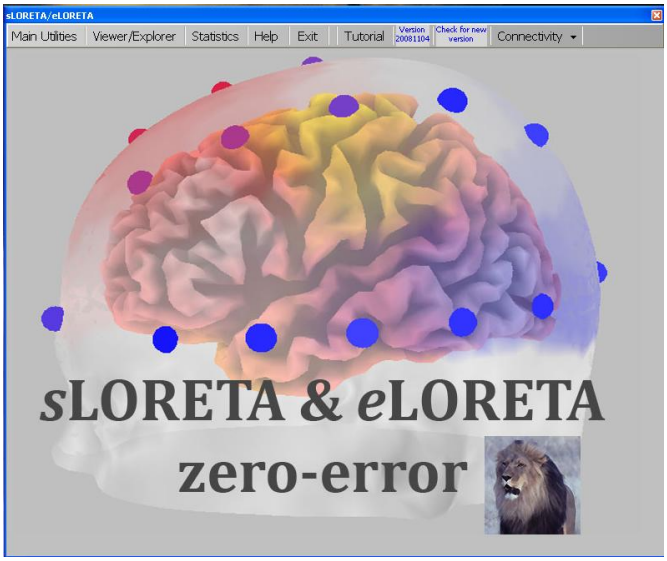


Figure 2.56 Capture of the sLORETA

2.4 Virtual Reality and Neuropsychotherapy

Once understood the main theoretical principles in which this Thesis is based (neuropsychotherapy, brain function and the main neuroimaging techniques for its study), a proposal will be formulated for improvement in the field. The hypothesis is that the use of virtual reality would help in the better assessment of the brain of subjects undergoing a psychological treatment. In this section, the principles of the virtual reality will be exposed, as well as a small introduction to what has already been done with VR in the field of Neuropsychotherapy.

2.4.1 Virtual Reality

2.4.1.1 Introduction to the Virtual Reality

Virtual reality is a technological system by means of which the real world can be emulated or it can be created a new imaginary one, using computer-developed environments that allow the user to see,

hear, sense and interact with the graphic three dimensional new-created worlds. The lived experience is called “virtual” because the stimuli applied to the subject are generated by a computer system.

The novelty virtual reality provides as technology is the ability of immersion and interaction. The immersion is produced thanks to the use of special devices. This way, the user has the feeling of physically being present in the virtual environment. The interaction is produced because virtual reality is not a passive visualization of the graphic representation, but an interaction between the user and the virtual world in real time.

There are a lot of VR systems, from videogames consoles available to the general public to more advanced visualization systems available just for big companies and research institutions.

Apart from the visual component, it is important to incorporate devices that allow the interaction in real time with the environment, in order to increase the virtual emotion.

Regarding the devices needed for the virtual experience, they can be distinguished in input and output devices. Input devices are those that allow the user to communicate with the VE; they can be as simple as a joystick or more complicated as a data globe which captures each movement of the fingers or a tracker which captures the body movement. In case of use VR inside a MR machine, the devices must be adapted to their use inside a magnetic field (they cannot have any metallic piece in them). Between the output devices, the most important are those which show the environment to the user (visual devices), and can be less immersive such as a computer’s monitor, or highly immersive such as a VR helmet (“Head Mounted Display”) or a CAVE system. Working with MR, the devices have to be adapted to the magnetic field, just like the input devices.

There are a lot of advantages in the use of virtual reality as stimuli, instead of using real ones. One of the more important is that virtual

environments allow the recreation of certain experiences that would be impossible to reproduce with real stimulus. To put some examples, in phobic treatments the researcher could make the patient interact with the feared animal in a gradual way, depending on the person's evolution. In cases of motor rehabilitation, VR games allow making the task more amusing, which improves significantly the results obtained in the subject in less time and with less psychological effort of the person. Moreover, there are the studies conducted with augmented reality (AR), a variation of VR that allows the user to see the real world at the same time that it is "augmented" by virtual elements. As those, there are lots of other examples of applications in which the virtual reality makes the work of the researchers easier.

2.4.1.2 History of the Virtual Reality

Although there are previous examples of works leading to the development of virtual reality, the first clear example of it is the Sensorama, designed by the cinematographer Morton Heiling in 1962. This prototype was the materialization of his "Experience Theatre" described in the mid 1950s as a new way of seeing theater as an activity that could encompass all the senses in an effective manner, thus drawing the viewer into the onscreen activity. However, the term "virtual reality" is a bit older than that, and was introduced first also referring to the theatre by the playwright, poet, actor and director Antonin Artaud in his book The theatre and its double (1938).

The Sensorama included stereoscopic display, fans, or emitters, stereo speakers and a moving chair; along with five short films to be displayed in it. In it the user was able to experience how it felt to ride a motorcycle on the streets of Brooklyn, while feeling the wind on the face, the vibration of the motorcycle seat, a 3D view, and even smells of the city. However, it was too expensive to develop and the idea was rejected from the film industry.

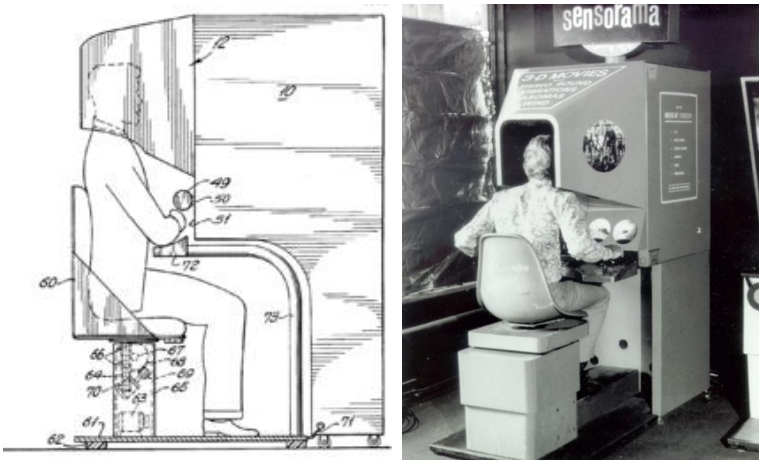


Figure 2.57 (a) Drawing of the Sensorama from its patent, (b) Image of the sensorama

The first head mounted display (HMD) was called Headsight and was developed by Philco Corporation engineers in 1961. It was thought to be used by helicopter pilots while flying at night. It consisted on a video screen and a tracking device, linked to a closed circuit camera system. Later, in 1968, Ivan Sutherland built the “Ultimate Display”, a HMD attached to a computer which allows the view of a virtual environment. However, the mechanism was still to be improved, being too heavy to be carried without a suspension device.

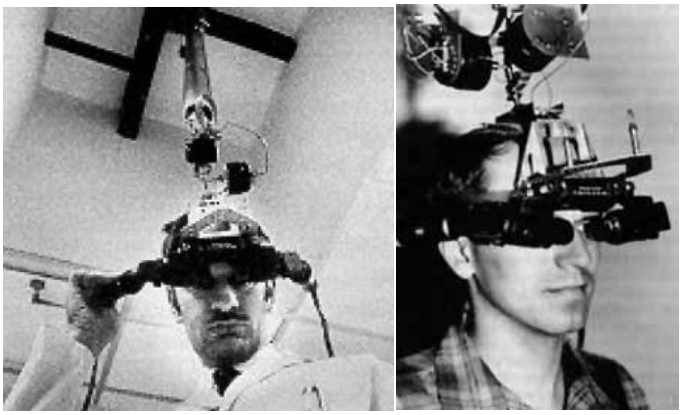


Figure 2.58 The “Ultimate Display” of Ivan Sutherland

The first interactive map was developed in the MIT in the 1970s, and consisted on a map of Aspen (the Aspen Movie Map) which enabled the user to walk through the town in three modes: summer, winter and polygons. While the first two consisted on photographs of the city, the third was a basic 3D model of it.

Figure 2.59 The Aspen Movie Map

Later in the 1980s, Jaron Lanier and Tom Zimmerman developed some of the first goggles and gloves systems to interact with the virtual environments. In 1991, Antonio Medina designed a virtual reality system to pretend the driving of Mars rovers from Earth in real time. After the 1990s, the popularity of the virtual reality systems decreased, although it is still widely used, normally referred to as "virtual environment" instead of "virtual reality" because of its negative connotations. More recently, the world of the videogames has re-launched the popularity of the VE and many enterprises have focused their developments in the improvement of the devices used for its control. For example, there can be mentioned the Oculus Rift, developed by Oculus VR, a new Head-Mounted Display which offers low latency and a wider field of view. This kind of devices can be combined, for example, with Razer Hydra sensors (developed by Sixense Entertainment and Razer USA), a kind of game controller with motion and orientation detection by means of a weak magnetic field,

which gives a precision for detecting the movements of 1mm and 1º, and which wireless version is in development.

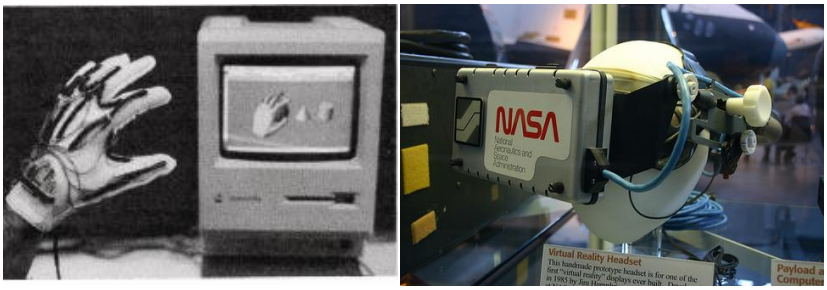


Figure 2.60 Images of data gloves and goggles designed by Jaron Lanier

2.4.1.3 Devices

There are lots of devices available for their use in VR, which can be divided into two main groups: input and output devices. The input devices, as aforementioned, allow the user to communicate with the environment; while the output devices present the stimulus to the subject. Now the main of them will be discussed in more detail.

Input devices

- Keyboard: it is a desktop input device, which allows the subject introduce simple discrete orders to the environment. They are cheap and easy to use, although they cannot be used in more immersive environments.

Figure 2.61 Example of a keyboard

- Mouse and trackball: like the keyboard, is a desktop input device, but this one allows the continuous introduction of data from the user (as well as discrete events from the buttons). The 2D mouse cannot be integrated in immersive environments, although the trackball can; they are cheap as well, and its use quite intuitive. Similar to the 2D mouse are the digital pads, which in its small format can be integrated in immersive VE.

(a)  (b)  (c) 

Figure 2.62 Examples of (a) a trackball, (b) a mouse and (c) a digital pad

- Joystick: one of the most used in VR for navigation and playing, they allow continuous and discrete movements, and are easy to use in 2D and 3D simulators.

Figure 2.63 Joystick

- Spaceball: they are similar to a mouse, but those tack 3D movements, following the translations and turns of the hand. The 3D is real, and not a translation from the 2D orders, but their use is more complex and difficult to learn.

Figure 2.64 Spaceballs

- Trackers: the trackers are input devices that follow the user's movements in the real world and translate them into movements in the virtual world. There are many kinds of tracker technologies: electromagnetic, mechanic, optic, ultrasonic, inertial, hybrids and even the eye-tracking which follows the movement of the eyes to locate the point where you look most.

Figure 2.65 Examples of different trackers

- Data Gloves: are a spetial kind of tracking devices that follow the movements of the hand and fingers of the user. There are two kinds of data gloves: bend-sensing gloves or pinch gloves. The bend-sensing gloves detect postures of the hand and certain gestures, while the pinch gloves detect when two or more fingers get into contact.

(a)  (b) 

Figure 2.66 Data gloves: (a) bend-sensing gloves, (b) pinch gloves

- 3D mouse: despite the 2D mouse, it follows the movement in 3D. It can be used with the hand, consisting on a joystick which position is tracked; or with just one finger, following its movement.

(a)  (b) 

Figure 2.67 3D mouse for being used with (a) the hand, and (b) one finger

- ShapeTape: there are optic fiber ribbons which allow controlling the movement of different parts of the body in a more flexible way.

Figure 2.68 ShapeTapes

- Biosignals: apart from the different mechanisms aforementioned to catch the movement, the orders can be given by voice using voice recognition systems and microphones or by bioelectrical signals from the body, such as BCI which catch the brain electric signals using EEG to command the environment.

Output devices

- Visual devices:
    - Desktop screen: the VR can be reproduced in a screen-based system, where the environment is shown in a common PC screen. For the 3D effect there can be used special goggles or 3D desktop screens. The main advantage of this system is that you can use computer devices such as mouse and keyboard, and is cheaper.

Figure 2.69 Desktop Screen

- Projection screens: the environments are projected in several screens, which size can vary depending of the design. The main advantage of those systems is the high immersive level achieved by them, especially in CAVE designs where you are surrounded by screens.

Figure 2.70 Projection Screens

- Workstations: similar to the projection screens, those normally use just one screen and it is mounted over a desktop or a wall. The main advantage is that they can be used by several people at the same time.

Figure 2.71 Workstation

- Head Mounted Displays: the device consists of two screens located near the eyes of the user; giving him a stereoscopic vision of the virtual world (the real world cannot be seen). There are bigger versions of

the same technology, but supported on the ground instead than over the head.

Figure 2.72 Head Mounted Display

- Auditory devices:
    - Headphones: are the most common and easy to use, allow reproducing different information in each ear, although they can be annoying and interfere with other devices.

Figure 2.73 Headphones

    - Speakers: they are strategically located in the room and the user does not precise to wear any other additional device, although they may attenuate the sound level with the objects of the room.

Figure 2.74 Speakers

- Haptic devices: they stimulate the touch sense and force models in the user. Can be referred to the ground or to the body, and stimulate the touch feeling, kinesthetic models or a combination of both.

Figure 2.75 Examples of haptic devices

2.4.2 Combining Virtual Reality with Neuroimaging

The studies that combine VR with some neuroimaging technique are diverse. Especially with fMRI, lots of studies have taken advantage of the benefits that VR can bring to the research. In the first studies, VR devices started to be adapted to allow their use inside the MR. For example, Baumann et al. (2003) developed a very advanced graphic environment which could be modified depending on the targets of the study developed each time, as well as the interaction of the subject with the VE and the use of a virtual map. They developed some devices specially designed for their use inside the MR to show the environment. In their study, they observed an increase in the activity of the motor areas (SMC, SMA and cerebellum), the attention areas (ACC), the areas related to memory (frontal, PFC and parietal) and vision areas (occipital and calcarine). A similar experiment was

conducted by Mraz et al. (2003), using data globes for the navigation. They developed two tasks: the first one using a common joystick and the second with the data globe. The introduction of the globes produced the activation of the primary sensorimotor contralateral cortex, as well as the motor areas, SMA and parietal regions. If it also included the possibility of watching the globe, the activation was even higher, especially in the ipsilateral parietal lobe.

Other studies have used fMRI to analyze the different brain activations achieved when real or virtual stimuli are applied. In this field, Han et al. (2005) studied 12 subjects using fMRI while they were exposed to photographs of: real people, drawings of people, drawings of robots and real animals. They concluded that the real stimuli activated the middle prefrontal cortex and the cerebellum, while the virtual stimuli activated the parietal cortex. In a similar study, this time developed with PET images, Perani et al. (2001) exposed the subjects to three tasks (first with 2D and then with 3D images): view of the movement of a real hand, view of the same movement but with a high-resolution virtual hand and view of the same movement with a low-resolution virtual hand. In 2D, the higher activation was achieved in the bilateral V5, cuneus and lingual gyrus; while in 3D the occipital cortex was the most activated area while seeing the virtual hands, not being activated during the task with the real one.

Some investigations have used VR as stimuli to analyze the brain activation during the performance of some specific tasks in the fMRI. Some studies have analyzed navigation and spatial memory. For example, Astur et al. (2005) made a research over the spatial memory, using as stimuli a virtual maze. There they found a decrease in the activation of the bilateral hippocampus during the spatial memory task, involved in the study of a radial-arms maze. Another remarkable example is that conducted by Pine et al. (2002) over the neural correlates of the spatial navigation using a VR environment as stimuli with different navigation conditions. Calhoun et al. (2005)

analyzed the influence of alcohol in driving, using a simulated drive in a virtual environment as stimuli. In another example, Lee et al. (2005) analyzed the reaction of smokers to tobacco-related stimulus, also using VE along which the users had to navigate.

Other studies have applied VR for different purposes, and have used fMRI to validate their results. You et al. (2005) analyzed the effects of the use of VR in the cortical reorganization and motor recovery associated to stroke patients, finding differences in the laterality index in the primary sensorimotor cortex between the control group and the VR group. Hoffman et al. (2003, 2004) investigated the neuronal correlates observed during the use of VR as pain distractor. Their results showed decreased activation levels in the pain-related brain areas when the VR stimuli where shown (Figure 2.76). This kind of therapy helps, for example, with burned patients, showing them environments to induce the sensation of cold. What's more, this study concluded that thanks to the low conscious attention of the human being, the distraction can be made by a simple environment, keeping the pain in a second plane.

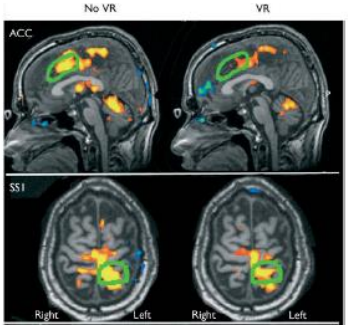


Figure 2.76 Results for the study of Hoffman et al. for some brain areas, before and after the VR application

2.4.3 Virtual Reality Exposure Therapy (VRET)

In the field of psychological treatment, the exposure therapy is widely used. It involves confronting stimuli that provokes fear or anxiety in the patient. The addition of the virtual reality to this setting allows the creation of a safe virtual world where the patient can

experience new realities without feeling threatened, allowing him to approach situations in a gradual way (Baños et al., 2011), which attenuates the anxiety felt (Riva, 2010). If the patient avoids the situation or the feared object, the phobia is reinforced. However, each successive exposure to the situation reduces the anxiety by means of habituation processes. So the VR acts as an intermediate step between the therapist's office and the real world (Botella et al., 2006).

Figure 2.77 Example of Virtual Environment that can be used for exposure therapy in patients with acrophobia

According to this, VR can be seen as an advanced imagination system (Riva, 2010), which means that it is a medium as effective as reality to generate emotional responses. And what makes this possible is the sense of presence, which will be studied in the next chapter.

The idea of using VR for the treatment of psychological disorders was conceived in 1992 in the Human-Computer Interaction Group of the Clark Atlanta University (North et al., 1997b, 1998), and, since then has evolved quickly. The technique has been successfully applied for the treatment of different anxiety disorders, such as specific phobias (Parsons and Rizzo, 2008), anxiety disorders, mood disorders, or substance abuse disorders (Emmelkamp, 2000). One of the first disorders to be treated with VR was acrophobia (Rothbaum et al., 1995a, 1995b; North and North, 1996), in the Clark Atlanta University. They used a scenario consisted of a building with an

exterior elevator that could reach different heights from which the patient could go to a balcony and have a look. They found that after eight sessions with this environment, the patient began to feel more relaxed, even in a height equivalent to a 15th floor.

In the field of phobias, VR has been widely used, for the treatment of phobias as varied as flying phobia (Rothbaum et al., 1996; North et al., 1997c), small animals' phobia (Garcia-Palacios et al., 2002) and social phobia (Slater et al., 1999; Pertaub et al., 2002), including also telepsychology treatments (Botella et al., 2000).

Other disorders in which VR based treatments have been applied include panic disorder, agoraphobia, post-traumatic stress disorder (PTSD) and eating disorders.

The objective when designing an environment for the treatment of agoraphobia is to expose the patient to his most feared situations (Jang et al., 2000; Moore et al., 2002). Environments that also simulated physical sensations of patients during panic attacks have also been evaluated, showing that the use of this technique can be useful both in short and long term results (Botella et al., 2007).

Regarding the use of VR for PTSD treatment, most of the environments designed up to now have been developed for a specific kind of traumatic event, similarly to what happens with phobias. For example, Rothbaum et al. (2001) designed environments for war veterans from Vietnam, Difede and Hoffman (2002) for 11th September victims and Rizzo et al. (2006) for Iraq combatants.

However, another approach has been evaluated, consisting on the use of a generic environment that admits a personalization depending on the specific trauma the patient suffers. Technically, that supposes a great advantage, because it is not necessary to develop a new environment for each patient. This approach was started in the European Project named EMMA (Engaging Media for Mental Health Applications). The EMMA World used symbols and

personalized objects with the goal of provoking and evoking emotional reactions in the patients which could help them in the emotional processing of the trauma, in the context of a secure and protected environment (Rey et al., 2005). The results of the validation of the system showed that the behavioral-cognitive therapy with EMMA was as effective as the standard behavioral-cognitive therapy for treating these disorders. Better results in depression measures, social interference and relaxation intensity were obtained in the case of the EMMA world (Baños et al., 2011). An example of two appearances that the EMMA world can adopt during the experimental sessions under the therapist control is shown in Figure 2.78.

Figure 2.78 a) Beach of the EMMA World, b) Meadows of the EMMA World

Finally, eating disorders are a complex category that includes anorexia, bulimia and binge eating disorder. One of the most serious problems in this kind of disorders is the distorted perception of the own corporal image, which has a great influence on the rehabilitation process. This aspect is difficult to evaluate with traditional techniques. However, several proposes with VR have been presented to help in the evaluation and changing of this perception (Riva et al., 1998, 2006; Alcañiz et al., 2000; Perpiñá et al., 1999), with encouraging results.

2.4.4 Proposal of the combined use of VR and Neuropsychotherapy

As was stated in the introduction to this section, the hypothesis in this Thesis is that the use of virtual reality during the assessment of subjects with a psychological disorder would help in the better evaluation of the brain activation' patterns, and that this information could be used later to adjust the treatment to the specific needs of each patient. As aforementioned, VR has been widely used in the treatment itself, but not as a tool for the better assessment of the brain activations before and after the therapeutic process.

VR allows a better and more accurate approach of the subject to the stimulus we want him to face. This kind of approach would be almost impossible with real stimuli, due to the impossibility of measuring the brain activations in real life (for example, the inability to interact with real stimuli inside a fMRI device, or the movements that would bring noise to the EEG signal). Moreover, we have commented the security that VR brings to the environment, allowing the gradual exposure of the subject and the control of every characteristic of the virtual world. This would help during the assessment to activate the brain areas related to a specific stimulus, distinguishing them from the rest. The information extracted would help in the better treatment of the subject, according to the neuropsychotherapeutical theory.

For this Thesis, the proposal is to use virtual environments in the assessment of subjects with small animals' phobia (more precisely, spiders and cockroaches phobia), to check in the brain areas activated are the ones that have been previously related to the phobia. Moreover, the extra information due to the interaction of the subject with the environment would lead to the better understanding of the disorder and could help in the better development of the treatment.

2.5 Overall Conclusions

In order to summarize what has been exposed in this Chapter, there will be made some overall conclusions. As aforementioned, the main

goal of this PhD Thesis is the study of how virtual reality can help in the assessment of the brain functioning, in order to provide useful information for the adjustment of the proper psychological treatment, in what is known as neuropsychotherapy.

Until now, there have been presented the main characteristics of the different actors involved in the setting of this Thesis: the brain and its structure, the neuroimaging techniques that will be used, the principles in which neuropsychotherapy is based and the basis of virtual reality. Hereafter, the works that have been conducted will be presented, grounded in the knowledge aforesaid.

Before being able to pursue this goal, two questions have to be answered:

1- Which neuroimaging technique is better for what is looked for in this Thesis?

2- Do the virtual environments developed really stimulate the brain areas related to the phobia? Or what is the same, are the VE felt as present so the phobia is stimulated?

For answering the first question, there have been proposed (as exposed previously in this section) the use of two techniques: fMRI for a better spatial resolution of the brain areas involved, and EEG for a simpler setting, less intrusive to the subject in order to not distract his attention from the virtual environment.

As a response for the second question, it was concluded that a study of the sense of presence induced in the virtual environment will be necessary before analyzing the phobia.

Moreover, this same presence study will serve as an indicator of the intrusion caused by the neuroimaging technique used. That means that if the environment is felt as immersive enough, the neuroimaging technique chosen will not affect to the final brain activation results. For this, the sense of presence will be studied by

means of the two neuroimaging techniques proposed: fMRI and EEG; and depending on the results it will be decided which one is better for the phobia study.

3 Presence

As it has been stated in the previous section, before being able to connect the brain areas activated during the phobic task to the fear itself, there is a need to evaluate if the subject feels the virtual environment as real. This is what in virtual reality is known as presence. The traditional way for measuring this parameter is by means of validated questionnaires or physiologic measures such as the skin conductivity and the heart rate; more advanced neuroimaging techniques are rarely used for this purpose, despite the great advantage they would carry to the analysis of the brain areas activated when the subject feels he is present in the virtual environment. In this part of the thesis, the main theory about presence and virtual reality will be described as well as the main previous studies that have been developed in this area. Then, there will be presented the two studies conducted to measure the sense of presence with two different neuroimaging techniques: first with fMRI and then with EEG. Finally, the results from both studies will be discussed and some overall conclusions made.

3.1 Concept of presence

The sense of presence inside a virtual environment can be described as the feeling of being there, inside the environment, instead of in the room where the experiment is taking place (Sheridan, 1992; Baños et al., 2000; Sadowski et al., 2002; Slater et al., 1997). Presence refers to the process of discerning and validation of the existence of oneself in the natural world; a process that, according to Heeter (1992), is learned by the human beings since their birth.

Other definitions avoid the need of a subjective sense of presence, suggesting that the effectiveness of the couple perception-action between the user and the environment is enough to define presence.

Sanchez-Vives and Slater (2005) also pointed out that inside the virtual experience, you are at the same time conscious of the “place” and the “events” and simultaneously conscious of that there are no

such place or events; however, you still behave and think as if the place were real and the events were happening. As your consciousness of the differences between the real and virtual place and events blurs, the barrier between your mind and the VE diminishes, improving your interaction with the computer-generated world. And that is because, as Loomis (1992) remarked, “presence is a fundamental property of consciousness”. Therefore, it is unlikely to be unidimensional (Kim & Biocca, 2006). The International Society for Presence Research (2000) proposed that presence could be considered from several major dimensions, based on the findings of different studies in the matter. The first dimension is spatial presence, the subject’s belief that they are really inside the virtual environment. The second is sensory presence, which is related to the subject’s perception of the Virtual Environment (VE) as they would perceive the real world, divided into visual, auditory and tactile perception. Social realism refers to the subject’s perception that objects, events and people that appear in the virtual environment could exist in the real world. Engagement occurs when the subject feels the virtual environment to be involving. Finally, social presence refers to communication with other people or entities inside the VE.

Inside Virtual Reality, there are two concepts to consider: presence and immersion. Presence refers to the feeling of being in the virtual environment, while your body is physically located elsewhere. However, the immersion concept refers to the technical ability of the system to offer a convincing and involving environment with which the subject can interact (Schubert et al., 2001; Biocca and Delaney, 1995).

The concept of presence is also important from the point of view of Human-Computer Interaction (HCI), helping in the improvement of the virtual environment’s design as well as in the measure of the influence those improvements have over the subject. If the sense of presence inside the VR increases, it means that the interaction between the computer-generated virtual world and the subject has

improved. In words of Riva et al. (2003), “as media becomes increasingly interactive, perceptually realistic and immersive, the experience of presence becomes more convincing”. What’s more, as Sjölie et al. (2010) remarked, “measuring brain activity while interacting naturally with a system makes it possible to correlate activity in specific brain areas, or patterns of activation in distributed networks, to hidden cognitive states, such as mental workload, and in turn relate these hidden states to aspects of the interface and the interaction”. The final aim of the HCI is the development of systems able to minimize the barrier between the human cognitive model of what the user wants to achieve and the computer’s understanding of the task performed by the user (Sharp et al., 2007). If those neural correlates hidden behind the sense of presence can be found, it may be possible to develop adaptative Brain-Computer Interfaces (BCI) which allow the changing in the environment depending on the needs of the users, vanishing the technology from the subjects’ awareness (disappearance of mediation), one of the main characteristics the virtual environment has to accomplish to make the experience satisfactory (Riva et al., 2003).

This “vanish” of the technology from the subject’s awareness is what will help in the development of environments able to stimulate the targeted psychological disorder as if it were presented a real stimulus, and guide the therapist in the underpinning of the brain areas related to the disorder. In the specific case developed for this Thesis, before being able to measure the brain areas related to the phobia inside a virtual environment, it is needed to verify that the subjects actually feel present inside the virtual world. If the subject feels that he is present in the environment, during the view of the phobic stimuli he will react as he would in a real situation and the brain activations would be considered as related to the phobia.

3.1.1 Measure of presence

There exist several ways of measuring presence in a virtual environment; however, not all are good. For being able to consider a

presence measure correct, it has to be (Sadowski and Stanney, 2002; Hendrix and Barfield, 1996):

- Relevant, having a direct link with the sense of presence
- Reliable, allowing the repeatability of the results
- Sensible to the changes occurred over the presence level
- Non intrusive, avoiding that its inclusion in the protocol degrades the sense of presence
- Portable, low cost and easy to learn and use

The measure of presence has been made traditionally using subjective techniques based on questionnaires (for example, Usoh et al., 2000; Witmer and Singer, 1998; Lessiter et al., 2001; Baños et al., 2000). To avoid the inherent problems of these kinds of measures, some objective measures have been proposed, mainly based on psychophysiological measures. For example, the skin conductivity or the heart rate are related to the anxiety level experienced by the subject, and can operate as a good indicator for the level of presence experienced in the environment (Dillon et al., 2000; Meehan et al., 2001). What's more, recent works have analyzed the sense of presence from a neuroscientific point of view, concluding that VR is not only a tool for neuroscience, but that the sense of presence in a VE is the object of study of neuroscientifics (Sanchez-Vives and Slater, 2005). In the subsequent sections there will be detailed the main characteristics of the most commonly used techniques for the measure of the sense of presence: questionnaires, physiological measures and brain image techniques (Transcraneal Doppler, EEG, PET, fMRI…).

3.1.1.1 Questionnaires

Questionnaires are the subjective way that has been traditionally used for the measure of presence (Usoh et al., 2000; Witmer and Singer, 1998; Lessiter et al., 2001; Baños et al., 2000). They are considered subjective because they analyze the level of presence experienced as a result of the exposure to a virtual environment once it has finished, mediating several tests the subjects have to fulfilled a

posteriori. Because of that, the personal opinion and the character of the person influence the answers (the person can, for example, grade the questions higher in order to answer what they think the researcher wants them to). For this reason, the questionnaires have been often criticized. For example, Freeman et al. (1999) showed how instable they were. What's more, the presence questionnaires can only be used after the exposure to the virtual environments, so data of the temporal evolution of the sense of presence are not available.

Several solutions have been proposed to avoid the aforementioned limitations of the technique, allowing monitoring several variables during the virtual experience. For example, IJsselsteijn and Ridder (1998) made a continuous register of the measures during the VE exposition; on screen it was shown a control that subjects could move in real time to indicate their level of presence. In another example, Slater and Steed (2000) used a virtual counter that measured the transitions between virtual and real environments. Moreover, other qualitative measures such as out-loud thinking, interviews or group discussions were proposed to improve the results.

There exist numerous questionnaire models proposed to obtain better results, more accurate with the real measures. One of the most commonly used is the SUS questionnaire (Usoh et al. (2000) (an example of this questionnaire can be seen in Appendix 4). This questionnaire is based on several elements to grade according to a Likert scale between 1 and 7. The questions are variations of three aspects (Slater et al., 1995): the sense of being there of the subject, the level in which the environments become more real than reality itself to the subject, and the grade in which the environment is considered as a place visited more than as a group of images. The value of the sense of presence is measured as a mean of all the answers ("SUS mean") or as the number of answers with high punctuation ("SUS count").

3.1.1.2 Physiological measures

Another kind of measures, more objective and widely used in presence, are the physiological measures (Dillon et al., 2000; Meehan et al., 2001). There exist two kinds of objective measures: the behavioral and the physiological, but here there will be explained the second ones. The major advantage of the objective measures is that they are taken during the virtual experience and not at the end of it, so they can be used as real time monitoring during the task. What's more, instead of measuring directly the level of presence, they relate this with the grade of change produced over several parameters obtained during the physiological measures or during the behavioral observation.

The physiological measures are the objective measures more used. According to Dillon et al. (2000), in comparison with the traditional techniques, the more immersive experiences produce higher subjective rates of presence and more intense physiological responses. Following some of the more applied physiological measures will be cited:

- Cardiovascular parameters and skin conductance: On one hand, the skin conductance is measured using two electrodes located over the surface of the skin that measure a little current that passes through them, obtaining the skin resistance (using the Ohm's law, R=V/I), that is connected with the activity of the sympathetic system. On the other hand, the cardiovascular system is controlled by branches of the sympathetic and parasympathetic systems of the autonomic nervous system; normally measured by electrocardiography (ECG).
- Tracking of the eye movement: assuming the level of attention people have to a continuous flew of stimuli is related with the sense of presence.
- Surface electromyography to measure the muscular activity: it is based on the premise that if the user feels present in the

virtual environment, the physiologic response will be similar to that observed in an equivalent situation lived in the real life.

3.1.1.3 Neurologic measures: brain image techniques

Virtual reality, as aforementioned, has opened a wide new branch of applications and possibilities in the field of the neuroscience, the cognitive science and the psychology (Tarr and Warren, 2002). However, the concept of presence is in itself object of study using brain image techniques. The fMRI, despite being widely used with VR stimuli for the neuroscience research, has scarcely been used for the measure of presence. In the following sections the principal neuroimaging techniques to be used for that goal will be discussed.

TCD

One of the most recently applied techniques for the study of presence is Transcraneal Doppler (TCD). It consists in a non-invasive technique for the measure of the blood flow and pressure in the brain, by means of the transmission of high frequency waves (ultrasounds) and the reception of its echoes from the red globes in the blood. Two recent studies (Alcañiz et al., 2009; Rey et al., 2010a) used Transcraneal Doppler for the measure of presence during the navigation through a virtual environment. Their results showed changes in the blood flow speed during the moments associated with different levels of presence. In another work conducted by the same research group (Rey et al., 2010b), they took advantage of the high temporal resolution of the TCD for the study of the temporal evolution of the blood flow velocity signal (BFV), monitoring the greatest BFV value in the posterior arteries during a perception task.

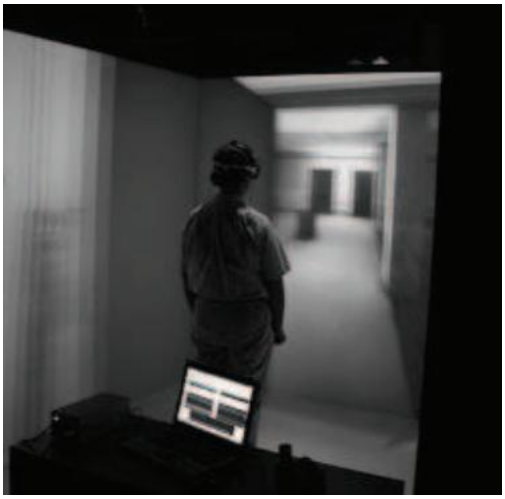


Figure 3.1 Photograph of a subject navigating through a virtual environment while the blood flow velocity is measured by TCD, from the study of Alcañiz et al. (2009)

EEG

Another technique for the measure of presence is the electroencephalography (EEG). As aforementioned in Chapter 2, the EEG measures the electric activity in the brain, more particularly the synaptic potentials in the cerebral cortex. The EEG signals represent potential differences between two electrodes, one active and another of reference. This technique has a temporal resolution of milliseconds, allowing the analysis of the EEG fluctuations depending on the task to accomplish. In this sense, it is worth to remark the work of Baumgartner et al. (2006), who evaluated the cerebral activity associated to the sense of presence using multichannel EEG, applying the low-resolution electromagnetic tomography technique (LORETA) for the study of the cortical structures that generate neurophysiologic activation. They compared the activation in children and teenagers during the view of a video of a roller coaster, and concluded that it stimulated the activation of the parietal areas of the brain, and that children have a higher sense of spatial presence than teenagers (less activation in the frontal area).

More recently, other studies were developed in interactive environments where the navigation through the virtual environments was allowed, in order to increase the sense of "being there". Kober et al. (2012) analyzed spatial presence in an interactive virtual world, comparing two systems for the presentation of the virtual stimuli: one based on a high-immersive VR wall (3D) and another based on a low-immersive 2D desktop screen. The 3D screen system showed a greater sense of presence associated with an increase in the Alpha band for the parietal TRPD ("Task-related power decrease"), related to the parietal activations. The lower presence experience in the 2D screen was accompanied by a strong functional connectivity between the frontal and parietal areas of the brain, pointing out that the communication between those areas is crucial for the experience of presence.

In another study, Kober and Neuper (2012) studied the Event-Related brain Potentials (ERP) of the EEG signal, which were elicited by tones that were not related with the VR experience and were used in the experimental design to obtain an objective indicator of the experience of presence in the virtual environment. They found a correlation between the increase in the presence experience and the decrease in the late negative slow wave amplitudes, related to the central stimulus processing and the allocation of the attentional resources. According to this conclusion, an increase in presence is related to a greater pay of attention to the virtual environment, which leads to a decrease in the attention paid to the irrelevant stimulus of the VR (decrease in the ERP components due to the tones).

fMRI

Combining presence with Virtual Reality and fMRI, there is the study of Baumgartner et al. (2008), who compared brain activation between children and adults while watching a video of a roller coaster, to identify the areas related to the sense of presence and the differences with the age due to the maturity of the brain. Despite

being only videos, they distinguished between the environments of high (Figure 3.2 left) and low (Figure 3.2 right) arousal, so the sense of presence was equally stimulated. The sense of presence was also measured by means of questionnaires. They concluded that some brain areas continue their maturation during the whole life, some of those related to the sense of presence. They explored the differences in activation between children and adults, in high and low arousal environments, to evaluate the previous results. As a result, they remarked the activation of the parietal lobe as one of the most important areas related to presence and to the egocentric spatial processing. Moreover, they obtained especially important activations in areas such as the cuneus, the middle occipital gyrus and the insula. Lastly, they remarked the existence of a negative correlation between the answers to the presence questionnaires and the brain activation in the dorsolateral prefrontal cortex (DLPFC).

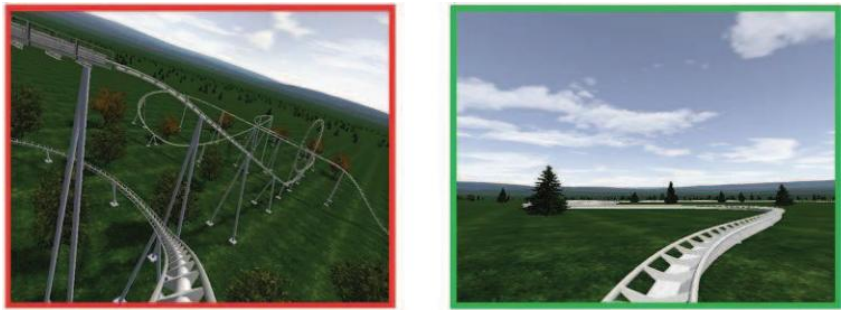


Figure 3.2 Captures of the environments for the high (left) and low (right) arousal situations, used in the study of Baumgartner et al. (2008) for the measure of the sense of presence

3.2 Experimental Study: Study of the sense of Presence in a Virtual Environment using different Neuroimaging Techniques

Once the theoretical framework of the sense of presence has been exposed, there will be explained the design of the study conducted for the measure of presence inside a VE. Both the fMRI and the EEG studies are based on the same experimental design, so the

explanation would be the same. Moreover, the common goals and methods for both studies will be presented.

The common target for both the fMRI and the EEG studies was to obtain the brain areas activated during the exposure to a VR environment, comparing different experimental conditions in order to obtain the areas related to the sense of presence. For this purpose, the task has been divided in three experimental conditions repeated in a counterbalanced order: view of photographs of the VE, view of a video of an automatic navigation along the same environment, and free navigation. The hypothesis is that the free navigation will generate a higher sense of presence over the subject than the other two conditions, using the comparison with the view of videos and photographs to remove those areas related to the mere stimulation of the visual areas.

In the present course of research, the main goal was to evaluate using brain imaging techniques if the sense of presence is stimulated when the interaction between the computer-generated environment and the subject is good. For this purpose, the brain areas that were activated in relation to the sense of presence during a virtual reality paradigm were studied.

It is known from previous studies that the sense of presence is influenced by the possibility of self-controlling the navigation (Welch et al., 1996; Alcañiz et al., 2009). In order to analyze the brain activation associated to changes in the level of presence, different navigation paradigms will be compared in the experimental design. Specifically, the brain activations during an experimental condition where the participants could navigate freely, will be compared with less immersive configurations (visualization of still images of the environment, and visualization of an automatic navigation – video – through the same environment). The selection of the three experimental conditions has been made based on the definition of Sanchez-Vives and Slater (2005) of the concept of presence as the ability to “do” inside the virtual reality, so the more you do inside the

virtual environment, the more presence you will feel. Comparing the conditions of free and guided navigation (video) it is expected to measure the differences in the level of presence due to the self-control of the movement; while the still-photographs condition will act as baseline condition. From this point of view, the increase of activity between the three experimental conditions would be translated to an increase in the sense of presence, losing the consciousness of the existing barrier between the real and the virtual world.

In order to ensure that there were differences in the level of presence between the different experimental conditions, the sense of "being there" was evaluated by means of a validated questionnaire (Usoh et al., 2000), that has been applied to obtain a subjective measure of the spatial dimension of presence in the different conditions and subjects. The main hypothesis of this research was that brain activation would be higher during a navigation task than during a video or photograph task in areas such as the cuneus and the parietal lobe, which are known to be related to presence from previous studies. Taking into account the results of Baumgartner et al. (2008), it was also expected to find negative correlations between the activation in the dorsolateral prefrontal cortex (DLPFC) and self-reported presence scores.

3.2.1 Virtual Environments

The virtual environments were programmed using GameStudio software (Conitec Datensysteme GmbH, Germany), which allowed the development of 3D objects and virtual worlds with which the user could interact and navigate. The virtual environment (VE) consisted of an everyday, clean bedroom (with a bed, a closet, and a desk with some books on it) where participants could navigate freely.

To allow the identification of the specific areas of the brain that were activated for each task, the paradigm was divided into three conditions developed with the same virtual environment: in the first, only photographs of the room could be visualized (4 photographs

displayed for 4.5 seconds each with 0.5 seconds of black screen between them); in the second, a video of an automatic navigation through the same room could be observed (with a duration of 20 seconds); and in the last one, the participant could navigate freely for 20 seconds in the VE.

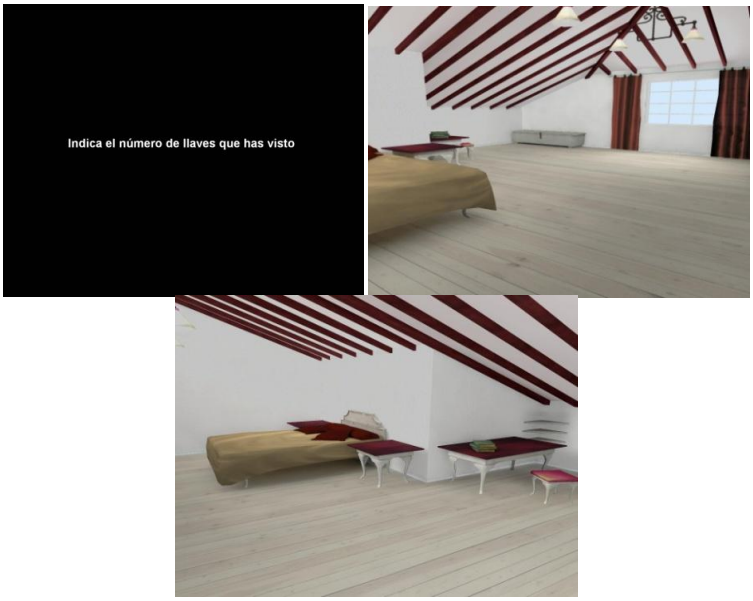


Figure 3.3 Captures of the environments used during the task

In order to prevent the subjects from staying still during the navigation period, they were instructed to perform a search task which forced them to move through the environment and kept them engaged with the stimuli. This task consisted in searching for some red keys that randomly appeared and disappeared in the environment, and counting the number of them that they had seen (maximum of 4, remaining in the VE for 5 seconds). They were not encouraged to find them all, or to find them as quickly as possible, they were only told to continue searching for them during each period. To prevent differences between the different phases of the experiment, this counting task was also performed during the other two conditions. During the photograph period, some of the images

showed featured keys and some did not, and the subjects had to count the number of keys they saw. During the video task, the keys appeared randomly in the environment as the camera moved through it. After each task, subjects were questioned about the number of keys they had found (they had to answer in a short period of 4 seconds). While they were conducting the tasks, the researcher checked that they had answered properly. The number of keys counted is not relevant, it was just included to avoid the subjects to remain still during the experimental conditions. Between phases, a black screen appeared to give subjects a rest period during which brain activation could decay to its baseline values (6 seconds) before the label indicating the next task appeared (2 seconds). The total time between tasks was 12 seconds. At the beginning of the experiment there were 14 seconds of black screen to compensate for T1 saturation effects. Each of the three experimental conditions was repeated six times in a counterbalanced order to prevent effects produced by the order in which they were presented. The total time of the complete experiment was 12 minutes 52 seconds. A scheme of the protocol can be seen in Figure 3.4.

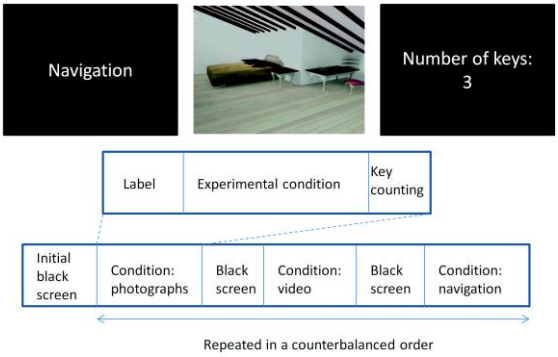


Figure 3.4 Diagram of the experimental design

To learn about the tasks that had to be performed inside the scanner room, subjects underwent a prior training session where they were introduced to the VR navigation and to the tasks. They were also

shown the differences between the photographs, videos and navigation, and practiced the hand movement using the joystick as it was going to be done during the scanner session. This training session was conducted in a supplementary virtual environment to prevent habituation.

Figure 3.5 Captures of the training environment

In order to prevent differences in activation caused by the motor task, subjects were instructed to move the joystick continuously during the video and photograph tasks in the same way as they did during the navigation period. The joystick movement was made just to compensate the brain activations caused by motor tasks between the different conditions. During the fMRI scan, the VR application checked the total time that they spent moving the joystick in each condition to guarantee that the motor movements had been continuous in all the cases.

3.2.2 Study of the Sense of Presence in a VE with fMRI

3.2.2.1 Materials and Methods

3.2.2.1.1 Subjects

For this study, there were recruited 14 right-handed women, none of them with any medical or psychological disorders, aged between 19 and 25 (mean age 21.64). They were chosen women because they are more expressive with their feelings and their brain activation is, therefore, greater (Canli et al., 2001; Lang et al., 1998). The

participants' hand dominance was tested using the Edinburgh Handedness Inventory (Oldfield, 1971), which can be seen in the Appendix 3. All these women were Spanish-speaking students, were paid for their participation in the study and were recruited from the Universitat Jaume I in Castellón and the Universitat Politècnica de València. Each subject signed a written informed consent prior to participation. None of them had to be excluded due to movements or distortion during the fMRI scan.

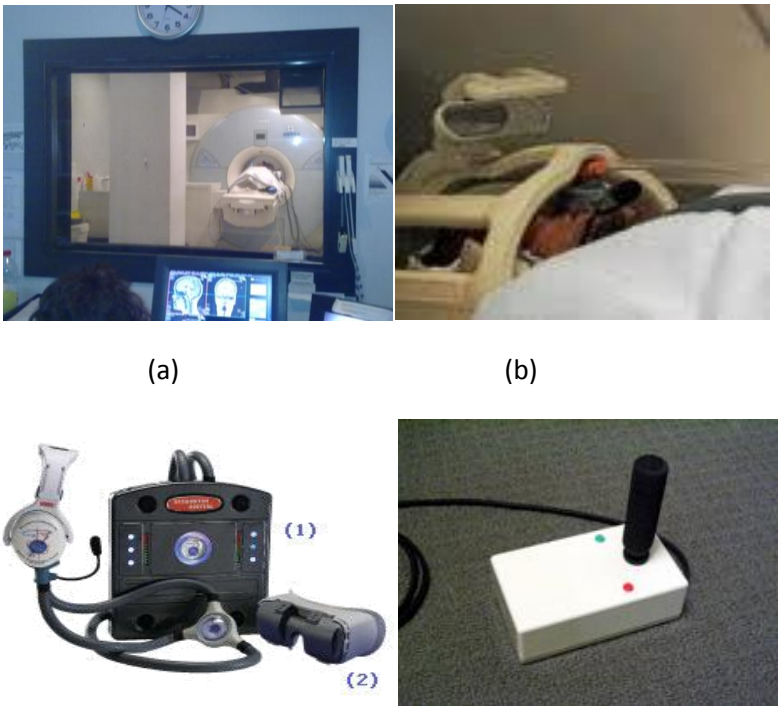
3.2.2.1.2 Post-fMRI questionnaires

In order to obtain numeric values to correlate with the results from the fMRI scan, after the scanner session the subjects had to answer several questionnaires. Questionnaires, as aforementioned, are the traditional method for the measure of presence inside VR. The questionnaires the subjects had to fulfill in this study were SUS questionnaires (Usoh et al., 2000), which evaluate the level of presence that they felt during each task. The questionnaire consisted in six, 7-point Likert type questions that had to be answered depending on the strength of the "being there" sensation experienced, where 1 corresponded to not feeling there at all and 7 to the highest sense of being there (as experienced in the real world). A midscale value of 4 would correspond to an intermediate level of being there, experienced by the subject as the midpoint between the feeling in the real world and not feeling there at all. Subjects had to complete 3 questionnaires, one for each task, all containing the same questions. An example of these questionnaires can be seen in Appendix 4.

3.2.2.1.3 fMRI Procedures

All subjects were scanned in a 1.5 Tesla Siemens Avanto Magnetic Resonance scanning device (Figure 3.6(a)) located in the General Hospital of Castellón, Spain. In order to prevent the movement of the head during the scan, an adapted magnetic resonance (MR) helmet (Figure 3.6(b)) was used. To display the environments, MRI-compatible video goggles we used, specifically, VisualStim Digital

(Resonance Technology Inc., Los Angeles, USA), an image of which can be seen in Figure 3.6(c); and, for the navigation, an adapted joystick was used (Resonance Technology Inc., Los Angeles, USA), that can be seen in Figure 3.6(d).



(a) (b)

(c) (d)

Figure 3.6 Photographs of (a) the magnetic resonance room with the Siemens Avanto 1.5T device, (b) an example of a helmet for the fixation of the head inside the resonance, (c) the goggles used for the view of the environments and (d) the joystick used for the navigation.

The followed protocol consisted on one first step were all the subjects were interviewed by phone to assure they all were right-handed and were suitable for the performance of a fMRI scan. Then they were given a date for the scan. When they arrived, they were conducted to a separate room where they performed the training session and were given the instructions to understand the task they had to perform. They also fulfilled a questionnaire to assure their

hand dominance (Edinburgh Handedness Inventory questionnaire (Oldfield et al., 1971), see Appendix 3). Once they had understood everything and signed the informed consent, they were conducted to a room where they could change their clothes before they entered the magnetic resonance room. Inside the device room, they were lain down inside the scan, where some technicians put the goggles, the helmet and the joystick on them. Once everything was all right, the scan began.

First, as is indicated for fMRI studies (Amaro and Barker, 2006), there were acquired the sagittal T1-weighted structural images of the brain (224 x 256 matrix covering the brain with 176 contiguous 1 mm slices, repetition time (TR) = 11 ms, echo time (TE) = 4.94 ms, flip angle (FA) = 15^{o}, voxel size = 1.04 x 1.04 mm). Then the functional scanning was launched, synchronized with the virtual environments. Functional images were obtained using a T2* single-shot echo-planar imaging (EPI) sequence. There were used 30 contiguous 4.2 mm interleaved axial slices (parallel to the line between the anterior and the posterior commissures or AC-PC line) covering the entire volume of the brain with a 64 x 64 matrix (TR = 2000 ms, TE = 30 ms, FA = 90^{o}, voxel size = 3.5 x 3.5 mm).

3.2.2.1.4 Data Analysis

3.2.2.1.4.1 Questionnaire Analysis

First of all, the data obtained from the SUS questionnaires were analyzed, using the program SPSS 17.0 (IBM Corporation, Somers, New York, USA). Apart from the individual responses to the six questions associated with each of the periods (photographs, video and navigation), it was calculated an additional measurement: SUS mean. This is the mean score across the six questions, that has already been described in previous studies (Usoh et al., 2000). A non-parametric Friedman Test was applied to compare SUS responses (dependent variables: questions 1-6 and SUS mean) for the different experimental conditions: photographs, video and navigation. After that, two by two comparisons between the three experimental

conditions were made. The post-hoc tests were made with a Wilcoxon Signed-Rank test with Bonferroni correction.

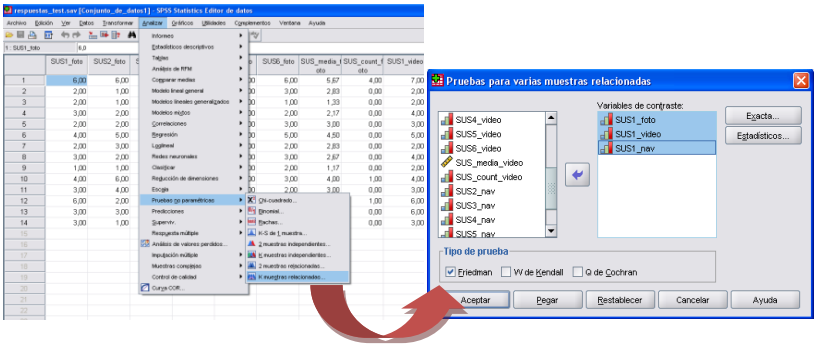


Figure 3.7 Captures of the SPSS program

For a greater robustness of the questionnaire results, a comparison was made, using a repeated measures test, between our results and those obtained in a previous work with similar experimental conditions conducted using TCD by the LabHuman group. In that study (Alcañiz et al., 2009), the level of presence was measured during two conditions: free and guided navigation. With this comparison it was evaluated the influence of the dependent variable (SUS mean) over the intra-subjects factor (experimental condition: navigation vs. video) and the between-subjects factor (fMRI vs. TCD). For the evaluation of the homocedasticity, the Levene's statistics were used.

3.2.2.1.4.2 fMRI Analysis

To analyze the fMRI data it was used the Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK), launched with Matlab Version 7.1 (MathWorks, Natick, Massachusetts, USA). The first 7 scans were excluded from the analysis to eliminate the decay of the fMRI signal associated with the moment when magnetization reaches equilibrium. The first step was to align the images to the AC-PC line.

Then the preprocessing began (Friston et al., 1995), realigning the functional images (estimate and reslice option). Once the realigned

functional images were obtained, the next step was coregistering them to the structural images, using for this functions based on the Information Theory (entropy).

When the coregistering was done, it was performed the segmentation of the result ("Segment") to obtain the gray matter, white matter and cerebrospinal fluid images. Then the resliced functional volumes and anatomical volumes for each subject were normalized separately with the normalization parameters extracted after segmentation. Finally, the images were smoothed using an isotropic Gaussian kernel or three-dimensional Gauss Bell (FWHM of 8 x 8 x 8 mm).

Once the preprocessing had been done, the next step was to conduct a first level fixed-effect analysis (with the aim of detecting changes in the BOLD signal between conditions in a single subject), where the individual contrasts comparing between the different experimental conditions were obtained. As a result, the "navigation>video", "navigation>photographs" and "video>photographs" contrasts for each subject were obtained. A 128 s high pass filter was also applied to eliminate the low frequency components in the signal caused by scanner motion and warming.

Group tests were performed at second level random effect analysis, where the group of subjects is taken into account. In accordance with the results obtained in previous similar studies (Pine et al., 2002; Baumgartner et al., 2008), the data were tested for task related activation by performing a one-sample t-test including contrast images of estimated parameters from all the subjects for the differences of interest between conditions. In total, three one-sample t-test were performed, for the contrasts "navigation>video", "navigation>photographs" and "video>photographs". Results from statistical tests at group level were considered significant if 10 or more adjacent voxels passed the statistical threshold of $p < 0.001$ (uncorrected).

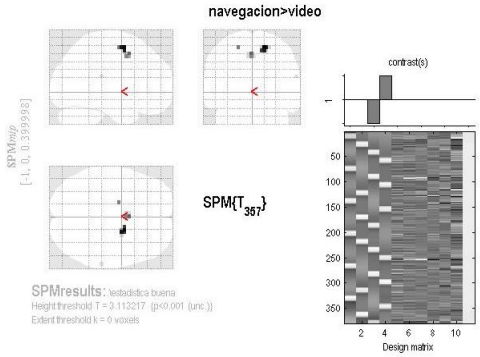


Figure 3.8 Capture of an example of brain activation for the "navigation>video" contrast and the design matrix

The aim was to look for activations in areas related to presence and navigation, such as the parietal lobe, the cuneus or the precuneus. To obtain the specific brain areas that were activated in each contrast, the xjView (http://www.alivelearn.net/xjview8/) software utility for SPM was used, which uses the MNI coordinates system.

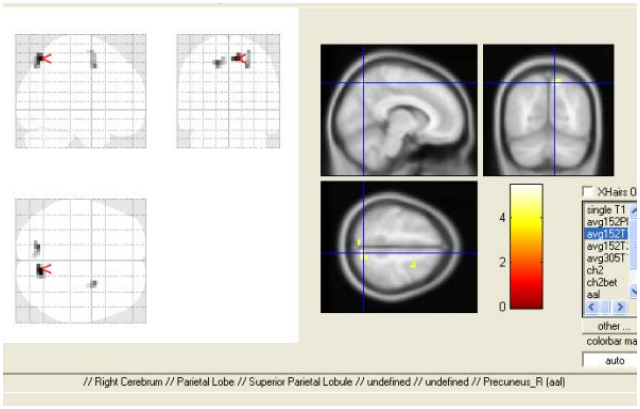


Figure 3.9 Capture of the results obtained with the xjView program

Once the brain activation maps for each group level contrast were obtained, a second-level multiple regression analysis was conducted to evaluate the relation between brain activation between conditions of interest and the subjective scores from the questionnaires. Three new group level analysis (for the three contrasts of interest:

"navigation>video", "navigation>photographs" and "video>photographs") were performed, where the differences between the SUS mean results for the experimental conditions compared in the contrast (see Baumgartner et al., 2008) were used as covariate. The covariate then was a vector of 14 components, one for each subject. The value of the component of each subject was obtained subtracting the value of the SUS mean for the second condition of the contrast compared from the value of the SUS mean of the first condition of the contrast. For example, the main interest in this study lay in the "navigation>video" contrast, where it was obtained the correlation analysis between the "navigation>video" contrast and the responses from the SUS questionnaires for the "navigation SUS mean score – video SUS mean score".

Finally, the brain areas that showed a linear parametric modulation of the activation levels and their associated subjective level of presence (SUS mean of each condition minus the global SUS mean) for the three experimental conditions (navigation, videos and photographs) were studied, according to increased sense of presence (following a procedure described in previous studies, such as Scheibe et al., 2006; Geake & Hansen, 2005; Smith, 2004).

3.2.2.2 Results

3.2.2.2.1 Questionnaire Results

As aforementioned, the subjects were asked to fulfil three questionnaires after the fMRI scan, one for each of the experimental conditions. The answers to the SUS questionnaire showed between subject variations. As sense of presence is subjective, each person can experience the conditions with a different grade of affectation. Some subjects found the environments quite immersive, while another did not believe the virtual illusion, and all this was reflected on the questionnaires. Some of the volunteers experienced the sense of presence as expected in the experiment design, with a lower sense of presence during the photographs task, medium in the video task, and higher during the navigation. However, some other subjects

found the video and navigation tasks quite similar, because the movement of the camera during the video fits the movement of the joystick, as will be explained later. There were also subjects that did not found the environments realistic at all, and scored the three tasks with low values. Mean values in each condition are shown in Table 3.1. There can be seen the mean values and the standard error for each question, as well as the SUS mean.

	Photographs	Video	Navigation
Question 1 SUS	3.1429±0.39023	3.7857±0.44695	4.4286±0.42857
Question 2 SUS	2.7857±0.48242	3.1429±0.47875	3.5000±0.50000
Question 3 SUS	2.0000±0.31449	2.5000±0.41603	3.1429±0.49009
Question 4 SUS	3.1429±0.37588	3.1429±0.49009	4.0714±0.45045
Question 5 SUS	3.4286±0.44121	3.5000±0.41603	4.0000±0.45694
Question 6 SUS	2.7143±0.36956	3.0000±0.50274	3.5000±0.53195
SUS Mean	2.8693±0.33034	3.1788±0.40368	3.7733±0.42555

Table 3.1 SUS responses of the questionnaires for each task (mean and standard error of the mean for the 14 subjects)

As it can be observed from the Table 3.1, the mean value of all the answers for the photographs task is 2.87, having all the individual answers a value bigger than 2. For the video task, the total mean is greater that the former (3.18) and all the questions have values over 2.5. At last, during the navigation the total mean is 3.77, even greater than in the other two tasks, with individual values for each question over 3.1. Those values agree with the former expectative of a growing sense of presence between the three experimental conditions. The results for the SUS mean can be graphically seen in the Figure 3.10.

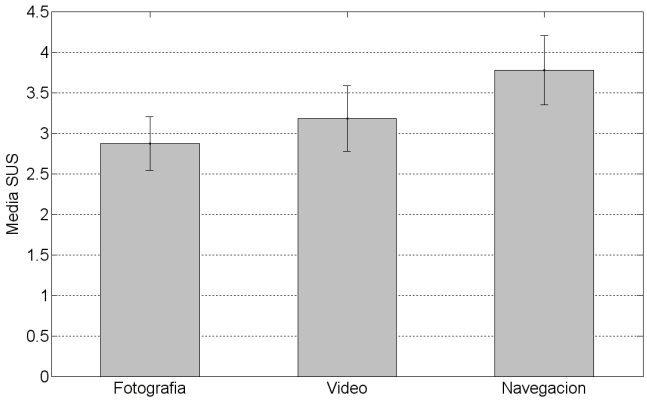


Figure 3.10 Results of the SUS mean for the photographs, video and navigation tasks (mean value and standard error of the mean)

Using SPSS, a non-parametric Friedman Test was applied to each question and the SUS mean for the three experimental conditions, obtaining significant differences between the three experimental conditions for all the questions except question 5 (results can be observed in Table 3.2). As can be observed from the results for each question, the greatest Chi-square value ($\chi 2 = 16$, $p < 0.001$) is observed for question 1.

	χ^2	p
Question 1 SUS	16.000	<0.001
Question 2 SUS	6.750	0.034
Question 3 SUS	10.903	0.004
Question 4 SUS	6.450	0.004
Question 5 SUS	5.250	0.072
Question 6 SUS	6.067	0.048
SUS Mean	12.293	0.002

Table 3.2 Results for the Friedman test for each question and the SUS mean

Post-hoc analyses based on Wilcoxon Signed-Rank Tests were conducted on the SUS mean results with Bonferroni correction, resulting in a significance level set at $p < 0.05/3=0.0167$ (the signification level is divided by the three experimental conditions). As can be seen in Table 3.3, there were no significant differences between the photograph and the video tasks ($Z = 1.174$, $p = 0.241 >$

0.0167). However, there was a statistically significant increment in the SUS mean in the navigation vs. photographs (Z = 2.805, p = 0.005 < 0.0167) and the navigation vs. video comparisons (Z = 2.550, p = 0.011 < 0.0167).

	χ^2	p
Photographs - Video	-1.174	0.241
Photographs – Navigation	-2.805	0.005
Video - Navigation	-2.550	0.011

Table 3.3 Results of the Wilcoxon test for the SUS mean

Regarding the comparison between the presence results obtained here and those obtained in a previous research conducted by people of the LabHuman group (Alcañiz et al., 2009) using TCD, there were taken into account just the data from those subjects who were women (9 out of the 32), to maintain the homogeneity in the results (SUS mean results can be seen in Table 3.4). In Alcañiz et al. (2009), the visualization of the virtual environments was done by means of a CAVE system, during two experimental conditions: free navigation and guided navigation (video). Applying the repeated measures analysis, with the SUS mean values as dependent variable, it was measured its influence over the intra-subjects factors (experimental condition) and between-subjects factors (image technique). As aforementioned in the Data Analysis section, to evaluate the homocedasticity Levene's statistic was used.

Subject	SUS mean navigation	SUS mean video
Subject 1	5.50	5.33
Subject 2	3.67	3.83
Subject 3	3.83	2.83
Subject 4	5.50	4.83
Subject 5	5.67	4.33
Subject 6	4.17	4.17
Subject 7	1.50	2.00
Subject 8	6.33	6.00
Subject 9	6.00	5.67

Table 3.4 Results for the SUS mean for each task in the Alcañiz et al. (2009) study

As a result, no significant differences were obtained with the inter-subject factor (F(1,21)=2.701, p=0.115). However, there were significant differences for the navigation factor (F(1,21)=11.598, p=0.003<0.005). At last, there was no interaction effect between navigation and the visualization technique (F(1,21)=0.751, p=0.396). A power analysis using the G*power3 program (Faul et al., 2007) showed that a total sample of 42 subjects would have been required to obtain the recommended 80% power in a t test comparison between fMRI and TCD, with alpha set at 0.05 and Cohen's d at 0.8 (large effect size).

3.2.2.2.2 Imaging Results

3.2.2.2.2.1 Contrast Results

The fMRI paradigm was divided into three different tasks (photographs, videos and navigation) that were compared to obtain the contrasting brain activations. The results for the three contrasts between tasks were obtained, the most relevant for the purposes of this study being those concerning the differences in activation between the free navigation and the guided navigation (video).

Results for the "navigation>video" contrast

The contrast "navigation > video" was selected and looked for the main activated brain regions. The results for the brain activated areas can be seen in Table 3.5. As observed, activations were found in the right cuneus (t=5.32, x=10, y=-91, z=26) and left parietal lobe (t=5.78, x=-47, y=-18, z=59) among others. Other brain regions activated in the "navigation>video" contrast were the right calcarine (t=5, x=24, y=-98, z=0), the right sub-lobar (t=5.28, x=27, y=-42, z=13) and the right insula (t=5.5, x=34, y=0, z=17).

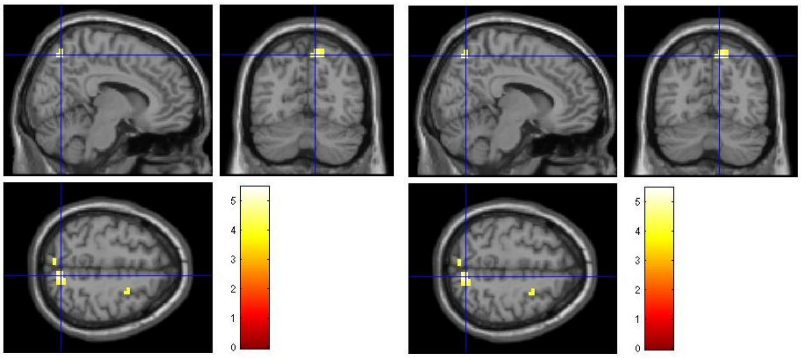


Figure 3.11 Captures of the brain activations for the "navigation>video" contrast; obtained with the xjView tool. (a) The image is centred over the right cuneus, (b) the image is centred over the left parietal lobe.

Anatomic Region	Hemisphere	x(mm)	y(mm)	z(mm)	t value	Cluster Size
Calcarine/ Middle occipital gyrus/ Occipital Lobe	R	24	-98	0	5.0042	22
Extra-nuclear/Sub-lobar	R	27	-42	13	5.2809	16
BA13/ Insula	R	34	0	17	5.4986	10
Cuneus/ Occipital Lobe	R	10	-91	26	5.3162	10
Postcentral/ Parietal Lobe	L	-47	-18	59	5.7771	19

Table 3.5 Results of the activated areas for the "navigation>video" contrast in MNI (Montreal Neurological Institute) space coordinates

Results for the "navigation>photographs" contrast

Regarding the "navigation > photographs" contrast, new activations were seen in the left cerebellum, both in the anterior (t=5.04, x=-43, y=-49, z=-37) and posterior (t=5.81, x=-8, y=-74, z=-25) lobes, and in the superior frontal lobe (t=9.82, x=24, y=0, z=55). There were activations in some areas of the occipital lobe, such as the cuneus (t=10.92, x=-22, y=-84, z=21), the left (t=9.95, x-26, y=-81, z=17) and right (t=7.60, x=31, y=-74, z=30) middle occipital lobe, and the right

lingual gyrus (t=6.80, x=3, y=-70, z=-5). Finally, activations were also found in areas of the parietal lobe, such as the precuneus (t=9.23, x=-22, y=-81, z=26). All these activations can be seen in Figure 3.12.

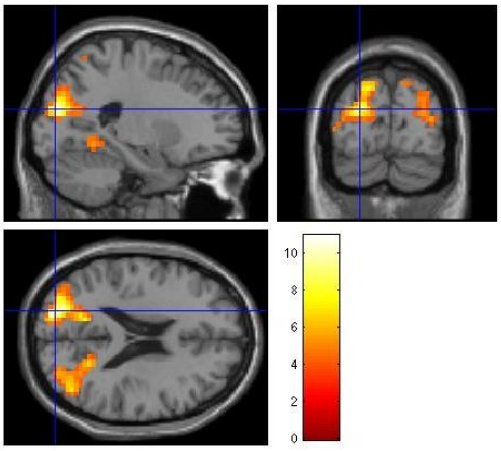


Figure 3.12 Capture of the brain activations for the "navigation>photographs" contrast, obtained with the xjView tool

Anatomic Region	Hemisphere	x(mm)	y(mm)	z(mm)	t value	Cluster Size
Cerebellum Anterior Lobe	L	-43	-49	-37	5.0356	56
Cerebellum Posterior Lobe	L	-8	-74	-25	5.8061	17
Superior and Middle Occipital Lobe / Cuneus	L	-22	-84	21	10.919	1085
Lingual/ Occipital Lobe	R	3	-70	5	6.7976	83
Superior Frontal Lobe	R	24	0	55	9.8225	143

Table 3.6 Results of the activated areas for the "navigation>photographs" contrast in MNI (Montreal Neurological Institute) space coordinates

Results for the "video>photographs" contrast

For the "video > photographs" contrast, activations were found in the right inferior temporal lobe (t=9.57, x=48, y=-70, z=-4), the right lingual gyrus (t=5.28, x=3, y=-74, z=0), the right inferior frontal lobe (t=5.99, x=41, y=11, z=21), the right supramarginal gyrus (t=4.83,

x=55, y=-39, z=30) and the right (t=5.91, x=27, y=0, z=51) and left (t=4.22, x=-29, y=4, z=51) middle frontal lobe.

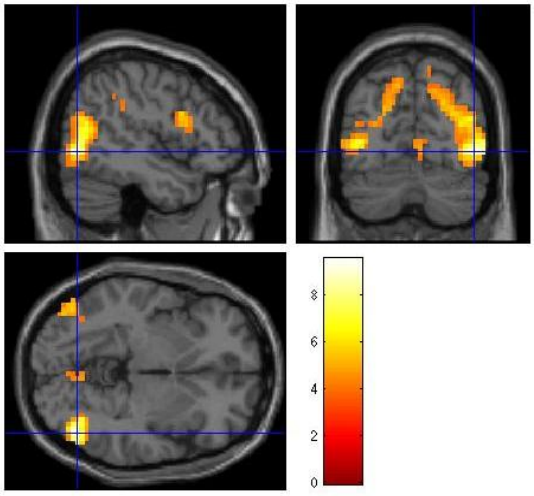


Figure 3.13 Captures for the brain activations for the "video>photographs" contrast, obtained with the xjView tool

Anatomic Region	Hemisphere	x(mm)	y(mm)	z(mm)	t value	Cluster Size
Inferior Temporal Lobe/ BA37	R	48	-70	-4	9.57	1147
Lingual Gyrus/ Inter-Hemispheric	R	3	-74	0	5.28	38
Inferior Frontal Operculum/ Sub-Gyral/ Frontal Lobe	R	41	11	21	5.99	44
Supramarginal Gyrus/ Inferior Parietal Lobe	R	55	-39	30	4.83	13
Middle Frontal Gyrus/ Frontal Lobe	R	27	0	51	5.91	73
Middle Frontal Gyrus / Frontal Lobe	L	-29	4	51	4.22	10

Table 3.7 Results of the activated areas for the "video>photographs" contrast in MNI (Montreal Neurological Institute) space coordinates

It is important to mention that with the inverse contrasts ("video > navigation", "photographs > navigation" and "photographs > video") no significant activation results were obtained.

3.2.2.2.2.2 Results for the correlations with the presence questionnaires

Regarding the correlation results, a second-level multiple regressions analysis was applied, where the correlations between the fMRI results and the questionnaire answers were obtained. For the "navigation>video" contrast, the results showed the existence of a negative correlation (Table 3.8) between the activation of the dorsolateral prefrontal cortex (DLPFC) of the right frontal lobe and the difference between the SUS mean values between navigation and video. In Figure 3.14 it can be seen a graphic that shows the correlation for the coordinates (48, 25, 17), corresponding to the right DLPFC.

Anatomic Region	Hemisphere	x(mm)	y(mm)	z(mm)	t value	Cluster size
Sub-gyral / Frontal Lobe	R	45	21	17	4.8747	21

Table 3.8 Results of the activated areas for the negative correlation in the "navigation>video" contrast

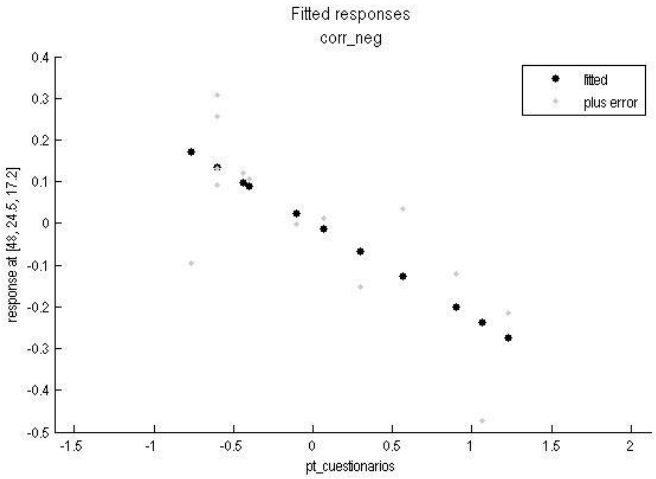


Figure 3.14 Graph of results for the "navigation > video" contrast, showing the negative correlation between the activation in the in the DLPFC (contrast estimates difference) and the questionnaire results (navigation SUS mean – video SUS mean). The color bar represents statistical t-values

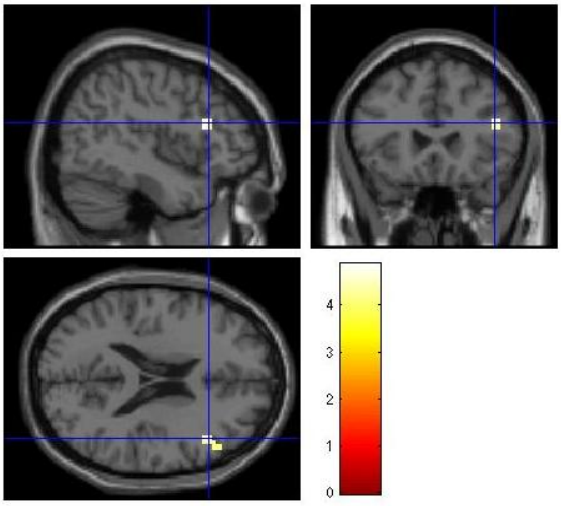


Figure 3.15 Image of the results of the negative correlation in the right DLPFC

On the other side, positive correlations were found in the left lingual gyrus, the left anterior lobe of the cerebellum, the left middle inferior temporal lobe, the left sub-gyral area, the left calcarine, the left superior temporal lobe, the left middle temporal gyrus and the left

cuneus. All these results can be seen in the Table 3.9. The Figure 3.16 shows the graphic of this positive correlation for the coordinates (-19, -53, 0), corresponding to the left lingual gyrus.

Anatomic Region	Hemisphere	x(mm)	y(mm)	z(mm)	t value	Cluster size
Lingual/ BA30/ Parahippocampal Gyrus/ Limbic Lobe	L	-19	-53	0	6.1862	114
Cerebellum_4_5/ Culmen/ Cerebellar Lobe Anterior	L	-19	-35	-21	5.763	18
Temporal_Mid/ Inferior Temporal Gyrus / Temporal Lobe	L	-61	-14	-21	5.9193	25
Sub-Gyral/ Temporal Lobe	L	-36	-11	-12	5.1038	14
Calcarine/ BA18/ Cuneus/ Occipital Lobe	L	-1	-91	9	5.044	13
Temporal_Sup/ BA42/ Superior Temporal Gyrus/ Temporal Lobe	L	-68	-28	9	5.3975	21
Middle Temporal Gyrus/ Temporal Lobe	L	-29	-74	17	4.6807	10
Cuneus/ Precuneus/ Parietal Lobe	L	-12	-74	38	5.7275	23

Table 3.9 Results in the areas activated for the positive correlation between the "navigation>video" contrast and the questionnaire results (SUS mean in navigation – SUS mean in video)

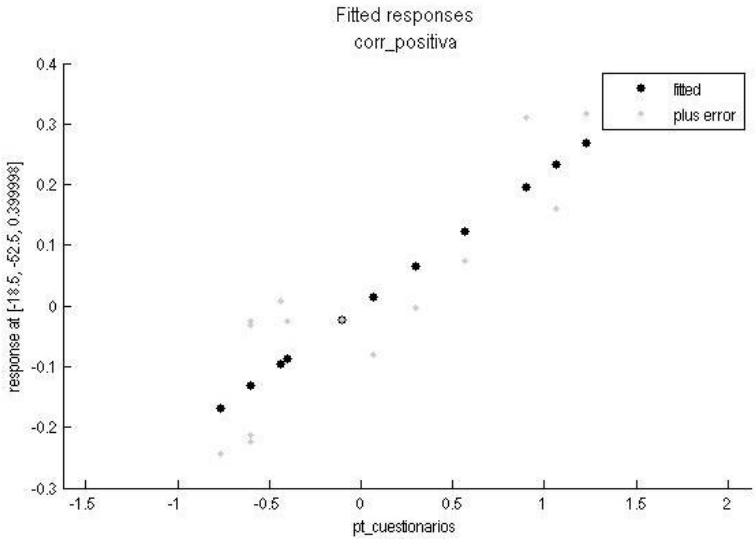


Figure 3.16 Graph of results for the "navigation > video" contrast, showing the positive correlation between the activation in the lingual gyrus (contrast estimates difference) and the questionnaire results (navigation SUS mean – video SUS mean). The color bar represents statistical t-values

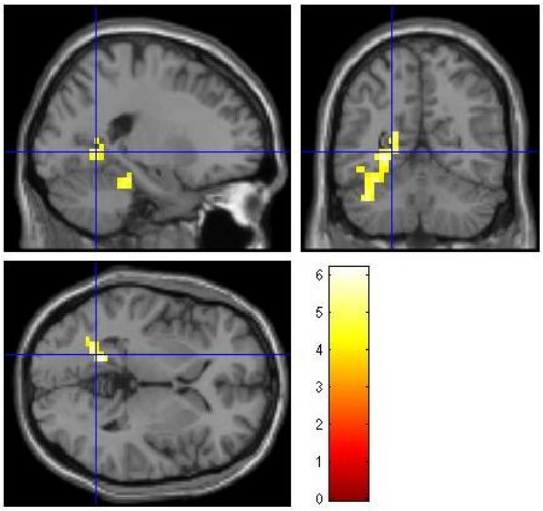


Figure 3.17 Image of the results of the positive correlation

3.2.2.2.2.3 Results for the parametric contrast

Finally, it was tested the possible existence of an increasing linear trend [-1, 0, 1] in the activation corresponding to the three reported levels of presence (SUS mean of each condition minus the global SUS mean values) according to the experimental conditions. The results showed that an increasing linear trend for the different presence-related conditions (photographs, videos and navigation) was observed in the activations in the right insula (x = 41, y = -14, z = 13; t = 4.22, p < 0.001, 10 cluster size) and the left postcentral parietal gyrus (x = -47, y = -18, z = 59, t = 6.67, p < 0.001, 10 cluster size) for the three experimental conditions (see Figure 3.18).

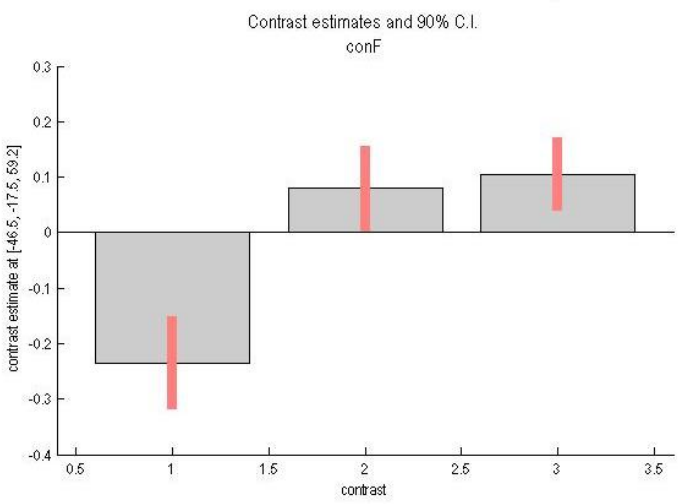


Figure 3.18 BOLD signal change in response to the different experimental conditions around MNI coordinates (-46, -18, 59), corresponding to the left parietal lobe. Observe the increase in signal between experimental conditions

3.2.2.2.2.4 Summary of the Imaging Results

In the following table (Table 3.10), a summary of all the results that have been presented in this section is presented. The first three columns correspond to the contrast results between the three experimental conditions; the fourth and fifth columns contains the results for the negative and positive correlations between the

"navigation>video" contrast and the questionnaire results; finally, the last column shows the parametric contrast's results.

Nav>vid	Nav>photo	Vid>photo	Neg. Corr.	Pos. Corr.	Param.
Calcarine R				Calcarine L	
Extra-nuclear R					
Insula R					**Insula R**
Cuneus R	Cuneus L			Cuneus L	
Parietal L	**Parietal (precuneus) L**				**Parietal L**
	Cerebellum L			Cerebellum L	
	Frontal (sup) R	Frontal (inf & med) L & R	Frontal (DLPFC) R		
	Occipital (med) L & R				
	Lingual sulcus R	Lingual sulcus R		Lingual sulcus L	
		Temporal R		Temporal L	
		Supramarg. R			

Table 3.10 Summary of the results for the fMRI study of presence

As can be observed in the Table 3.10, both the insula and the parietal lobe present a lineal increase of their activation between the three experimental conditions and are significantly activated for the "navigation>video" contrasts (the parietal lobe appears also in the activations of the "navigation>photographs" contrast). Moreover, the Calcarine and Cuneus, that are activated for the "navigation>video" contrasts, present a positive correlation with the questionnaire results.

3.2.2.3 Discussion of the Results

The principal aim of the present study was to analyze if subjects could feel presence while navigating in a virtual environment,

analyzing the results using fMRI. As aforementioned, if this is so, this would mean that the interaction between the computer-generated world and the subject is naturally performed and the barrier between technology and reality has been reduced. As mentioned previously, it was tried to generate an increase in the sense of presence between the different experimental conditions by means of the increase in the actions the user has to perform in the virtual environment. Presence was then especially motivated by the free navigation condition, where it is the user who controls the movement along the environment. This free navigation in a virtual environment was shown to induce a higher feeling of presence in the participants than a guided navigation condition (that in a comparison would act as the low presence condition). Contrasting the functional activation seen during these two conditions ("navigation > video"), results showed a higher activation of the parietal and occipital brain regions, including the cuneus, during the navigation condition, as hypothesized, but also activation of the right insula. These areas are included in the distributed network activated by presence that was described by Jäncke et al. (2009). Moreover, the differential subjective sense of presence reported by participants in the questionnaires between the navigation and video conditions, was shown to be inversely correlated to the activation of the dorsolateral prefrontal cortex, and directly correlated to the activation of the lingual gyrus and cuneus and other occipital and temporal regions. Finally, it was observed a linear increase in the activation of the right insula and left postcentral parietal regions according to the subjective sense of presence reported for each condition (SUS mean of each condition minus the global SUS mean values). Among the multiple brain areas activated by the "navigation > video" contrast, the cuneus and the post-central parietal lobe, which have been related to working memory and navigation tasks (Haldane et al., 2008; Mishkin & Ungerleider, 1982), can be highlighted. These results are comparable to those obtained in other presence studies that have been conducted using fMRI (Baumgartner et al., 2008), or can be extrapolated to the results obtained with other techniques such as TCD (Alcañiz et al., 2009) or EEG (Baumgartner et al., 2006), always considering the limited spatial resolution of these techniques. Regarding the "navigation > photographs" and "video > photographs" contrasts, they showed some similar activations, such as the lingual gyrus, the cuneus, the

frontal lobe or the occipital lobe. In this section, all these items will be discussed in more detail.

The subjects answered three SUS questionnaires (one for each experimental condition) where they evaluated the level of presence they felt. In each question, they value between 1 (not feeling there at all) and 7 (highest sense of "being there") the presence experience. The results confirmed that a higher level of presence was induced during the free navigation than during the photograph and guided navigation conditions. Furthermore, it was observed how the mean value for subjective sense of presence increased for each condition, observing the lowest score for the photographs and the highest score for navigation. Specifically, the Friedman Test showed significant differences between the experimental conditions for all the questions and the SUS mean except for question 5, which evaluated how the user remembered the experience in comparison to a real one. The largest difference between experimental conditions in response to the questionnaire was found in Question 1, which asked directly about the sense of being in the virtual world. Finally, post-hoc analysis based on the Wilcoxon Signed-Rank tests showed no significant differences in the comparison of the photograph and the video tasks, but that there were significant differences for the other two comparisons: photographs vs. navigation and video vs. navigation. Therefore, as hypothesized, there were significant differences between the level of presence experienced during the navigation condition and that experienced during the other two conditions. As indicated, a previous study by Welch et al. (1996) analyzed this connection between presence and navigation and their results are in accordance with the present study. They used two levels of interaction, the subject as an active or a passive driver, and observed that the interactivity increased the sense of presence the subject experienced. When comparing the results from this work with those obtained in a previous research about presence using TCD (Alcañiz et al., 2009), there were found similar presence levels in both studies, presenting a similar trend between both tasks. In fact, there were found significant differences between the conditions for both groups, but no differences between the groups were observed. There is only a trend (that does not reach significance) to higher presence ratings in the TCD research, probably due to the more immersive environment (the CAVE-like configuration) and the less intrusive

machine (the TCD probes). The magnetic resonance is noisy, requires you to be still and laid and makes difficult the feeling of "being there".

One purpose of this research was to test the hypothesis that functional magnetic resonance imaging is a good way to explore brain activation related to presence in a virtual environment when comparing between different experimental conditions, allowing to obtain objective differences in brain activation associated with the different levels of presence that the subjects have experienced. The main contrast that was analyzed was the "navigation > video" contrast, to evaluate the differences in brain activation between two conditions which induced different levels of presence, as measured with the SUS questionnaire. In the following paragraphs the results from this principal contrast will be analyzed in detail. As explained in the Results section, one of the most significant activated areas is the cuneus, part of the occipital lobe. This area has been related in previous works to the visual processing (Perani et al., 2001). The cuneus is known to receive visual information from the contralateral superior retina, and the processing which occurs in the area is modulated by other effects, such as attention, working memory or reward expectation (Haldane et al., 2008; Vanni et al., 2001). In this study, the cuneus activation is related to the subjective sense of presence experienced during free navigation in a virtual environment. Another region included in the results is the calcarine sulcus, also part of the occipital lobe where the primary visual cortex is concentrated (Le Bihan et al., 1993; Belliveau et al., 1991).

Another brain region which showed significant activation during the task was the post-central parietal lobe. Between the usual areas considered to be part of the presence network, the parietal lobe is involved in determining spatial sense and navigation, directly associated with the navigation in the virtual environment (Mishkin & Ungerleider, 1982; Johnson et al., 1996). Moreover, Mellet et al. (2010) found that left activation of the parietal lobe was higher while navigating through a virtual environment than while navigating through a real one. Activation was also found in the insula, usually related to emotion and the regulation of the body's homeostasis, including perception, motor control of hand and eye movements, self-awareness, cognitive functioning and interpersonal experience

(Karnath et al., 2005; Craig, 2009). As pointed out in the Introduction section, the most important of these items for this study are self-awareness, sense of agency and sense of body ownership, because they are closely related to the sense of presence experienced inside the virtual environment. The sense of body ownership allows you to discriminate your individual's own body and perceptions; forming the "body schema" which covers the dynamic distributed network of procedures aimed to guide your behavior (Haans and IJsselsteijn, 2012). The results of this study showed a parametric increase in the activation of the right insula according to the sense of presence experience in the conditions. Recent studies (Dodds et al., 2011) have found evidence that the right insula may be activated by a combination of attentional and response control demands, playing a role in the processing of sensory stimuli that are relevant to current goals. During navigation in a virtual world, decisions are constantly made based on evaluation of the sensory stimuli guiding our behavior in the virtual environment. The results in this study suggest that the insula may play a key role in guiding behavior in the virtual environment based on the presented stimuli and the sense of presence. Moreover, according to Sjölie et al. (2012), attention and behavior are essential to develop the sense of presence, increasing the precision in the predictions about the environment and the synchronization with it, and avoiding prediction errors from sources outside the VE.

All these results are consistent with those obtained in the Baumgartner et al. (2008) research. They generated different levels of presence by means of two different types of environment, one that induced a high arousal experience and another that induced a low arousal experience. They placed particular emphasis on the parietal lobe as one of the most important areas related to presence and egocentric spatial processing, something which was also observed in the results presented here. They also mentioned significant activations in the cuneus, middle occipital gyrus and areas involved in emotional processing, such as the insula; activations in these brain regions were also observed in this study and associated with the condition which induced the higher level of presence.

Although the results obtained in this study can be compared with those obtained in previous presence studies, those comparisons

should be done carefully. Each brain area is involved in several other functions not related with presence, and the network described before is not a closed one to the study of presence. The activation of those areas does not necessarily imply stimulation of the sense of presence. As Jäncke et al. (2009) explained, it is a network involved in the control of many other psychological functions, and "the psychological specificity cannot be inferred simply by identifying the activated brain structures". Moreover, the primary aim was to demonstrate the validity of fMRI as a tool to evaluate presence; not to map the brain network involved in its stimulation. The fMRI is a great tool to measure brain activity, but the size and characteristics of the machine makes impossible to use it in real situations. If it can be proved that the subject can feel presence inside a virtual environment visualized in the magnetic resonance, this could lead to the use of virtual reality to approach the subject to the equivalent real situation while being scanned. Moreover, as aforementioned, demonstrating that the sense of presence can be stimulated proves that the interaction between the computer-generated environment and the subject is performed naturally, making the technology "invisible" to the user. Obtaining activation in brain areas which have been previously related to presence is remarkable in the sense of showing that these results are not random, and that the initial hypothesis has been accomplished. The main objective of this fMRI research is then to bring into agreement with previous presence theories, not to show new results on the matter.

In a more theoretical perspective, the degree of presence in a virtual environment may be considered as the degree of synchronization between the environment and the subject's mental reality. In this case, the subjects view the VE for the first time in their lives during the scan, but due to the increasing familiarity of humans with virtual phenomena, this should lead to the internalization of mental simulations of the VEs, which matches with the activity theory so popular in the HCI circles (Sjölie, 2012). So the fact that the subjects are not familiarized with the environments should not prevent the sense of presence. Moreover, the central nervous system is capable to incorporate the new tools and technological artifacts that are used in the virtual experiences to its representation of the body schema, integrating them in a functional unity with our biological limbs and

sensory receptors (Haans and IJsselsteijn, 2012), helping the interface transparency or “disappearance of mediation” (Riva et al., 2003).

Referring to the search task the subjects had to perform inside the environment, it was designed to avoid them staying still during the experiences, but the fact of identifying an objective to perform inside the virtual world enhances a major sense of presence in the subjects (Riva et al., 2011). In fact, if the performer becomes “emotionally and intellectually engaged” by the task developed, higher levels of presence can be achieved (Waterworth et al., 2002); which leads to a state of loss of self-consciousness (Riva et al., 2011), as has been previously discussed.

The other contrasts evaluated in this study will now be discussed. As it has been previously stated, the results for the “navigation > photographs” contrast showed the activation of the cuneus and the parietal lobe, two of the most important results obtained in the “navigation > video” contrast, which were highlighted as having been previously related to presence during the navigation task. Moreover, the activation of the cuneus may reflect an increase in the visual processing due to the change in the optical flow between both conditions. It has also been found activations in the cerebellum and the frontal lobe, results that coincide with those obtained by Pine et al. (2002), who also evaluated differences between free and guided navigation. The cerebellum may have been activated because of its role in the control of movement (Wolf et al., 2009; Willshaw, 1999). The frontal lobe is related to the planning of the navigation task (Baumgartner et al., 2006; Owen et al., 1990). It is also important to remark that the cuneus, precuneus, middle occipital lobe and frontal lobes are areas which were also activated in the research by Baumgartner et al. (2008).

Regarding the “video > photographs” results, there are coincidences with the study by Pine et al. (2002) in the temporal and frontal lobes. The results from this study only agree with those from Baumgartner et al. (2008) in the middle frontal lobe, which is often referred as being involved in various executive functions as, for example, the planning of movement (Baumgartner et al., 2006; Owen et al., 1990). The fact that there are no other coincidences between the results may be explained by the lower sense of presence stimulated during

the two conditions (video and photographs) compared here. Moreover, inside the temporo-occipital cluster, it is worthy to remark the bilateral activation of the V5/MT area, part of the extrastriate visual cortex, which plays a main role in the perception of movement (Born and Bradley, 2005), due to the addition of visual movement in the video condition.

With regard to the correlation analysis comparing brain activation and responses to questionnaires, it was found a negative correlation in the prefrontal cortex, more specifically in the dorsolateral area, which agrees with the result obtained by Baumgartner et al. (2008) for the measurement of presence in video tasks, although at an inferior location within the DLPFC. This area is related to executive processing within working memory (Petrides, 2000) and controls the visual information that comes from the visualization of the virtual environment, being involved in the decrease of the sense of presence (Koechlin et al., 2003). Moreover, Jäncke et al. (2009) also remarked its importance in modulating and generating the activity of the network associated with the experience of presence. Regarding the positive correlations, there were obtained significant activations in the lingual gyrus, cerebellum; middle, sub-gyral and superior temporal lobe; calcarine and cuneus. All of these areas are related to sense of presence, which explains why their activation gets higher along with the increase of the questionnaires scores. Particularly remarkable is the result for the lingual parahippocampal gyrus, more specifically the activation of the parahippocampal area, a sub-region of the parahippocampal cortex related to spatial orientation and encoding and recognition of scenes (Aguirre et al., 1996; Epstein & Kanwisher, 1998).

Referring to the parametric analysis, it showed a lineal trend between the three tasks associated with an increased feeling of presence in the insula and parietal lobe, two of the most significant areas that were emphasized for the “navigation > video” contrast, and which are related to self-awareness (Karnath et al., 2005; Craig, 2009) and navigation sense in a virtual environment (Mishkin & Ungerleider, 1982; Johnson et al., 1996), respectively. The fact that these two areas showed a positive correlation with questionnaire scores, and in the parametric analysis, is an indicator of their relation to sense of presence.

To finish this discussion, some of the limitations of this study will be addressed. The study was conducted using a specific group of participants, namely 14 right-handed women. They were all right-handed to prevent noise effects of manual lateralization on brain activation in virtual/spatial processing. The subjects were all women to reduce variability generated by gender differences. There are some previous studies which show that women present a higher activation in the presence of emotional stimuli than men. In fact, Canli et al. (2001) indicated that they chose women because they respond more intensely to sensitive stimuli. They also maintained that women show a greater psychological reaction according to their value judgment than men. Some other studies concerning emotional arousal have also concluded that women demonstrate higher activation when shown disgusting images than when shown pleasant ones, while men do not demonstrate any difference (Lang et al., 1998). A great deal of previous studies concerning visual stimuli has been conducted with women (e.g., Dilger et al., 2003; Ochsner et al., 2002). Another limitation of this study was the small sample size, which restricts the statistical power to detect changes in the BOLD signal.

In this study, the continuous movement of the joystick was added to compensate the differences between experimental conditions in the activations caused by the motor tasks. However, there were differences in the active planning between the free navigation condition and the other two tasks, and these differences could not be prevented because they are one of the causes of the differences in the feeling of presence between experimental conditions. It should be also remarked as limitation the low significance level that was used for the statistical analysis of the fMRI data ($p<0.001$ (uncorrected) may be a liberal threshold). Maybe the use of a 3T scanner could improve the results obtained here.

In conclusion, the activation of the cuneus, the insula and parietal areas should be noted, especially the latter, due to its relationship with the navigational aspects of the VR experience. As has been shown in this section, the final results obtained are consistent with those from other studies concerning navigation in VR, presence in VR studied with other brain imaging techniques and presence during an

automatic navigation in a virtual environment studied with fMRI. Moreover, insula activation in VR and its parametric association with the sense of presence experienced in each of the conditions raises questions regarding its role in the virtual experience. However, the brain activation results may be seen just as a proof of the utility of fMRI as a tool to evaluate presence, and the important consequences that this could have in the field of the Human-Computer Interaction. Although in this study differences in presence have been generated with changing navigation conditions, possible future research could involve more arousing environments, with different content, to analyze other factors that can induce presence. Moreover, the demonstration that presence is related to measurable differences in brain activity, even inside an unfriendly environment as it is a magnetic resonance machine, opens the door to future studies combining virtual reality with fMRI for psychological treatments and psychopathological applications.

3.2.3 Study of the Sense of Presence in a VE with EEG

3.2.3.1 Materials and Methods

3.2.3.1.1 Subjects

For this study, 20 subjects have been recruited and equally distributed in two groups. The groups differed in the kind of screen used to display the environments: the first group viewed the environments on a common PC desktop screen (DS) and the second on a high resolution Power Wall screen (PW).

All the subjects were recruited from the Universitat Politècnica de València, were Spanish-speakers and were right handed. The participants' hand dominance was tested using the Edinburgh Handedness Inventory (Oldfield, 1971), which can be seen in the Appendix 3. For the first group (DS), 6 men and 4 women were evaluated, with ages between 22-29 years old. For the second group (PW), 5 men and 5 women underwent the study, with ages between 21 and 29 years old. They received economical compensation for their participation in the study.

Ethical approval was obtained from the authors' institution. All of the subjects provided signed consent for allowing their data being used in this study (see Appendix 2). One subject (a woman) from the DS group had to be excluded due to movement during the scan. The experiments were conducted in a laboratory inside the LabHuman group. The EEG signal was monitored by means of a multichannel wireless portable EEG device (Emotiv EPOC) (Rey et al., 2012), which has 14 data-collecting electrodes and 2 reference ones. The handset transmits wirelessly the EEG data to the computer.

	DS-Emotiv EPOC	PW-Emotiv EPOC
Ages	22-29 years old	21-29 years old
Men/Women	6 men/4 women	5 men/5 women
Excluded	1 woman	None

Table 3.11 Summary of the participants' data

3.2.3.1.2 Post-EEG Questionnaires

After the EEG session the subjects had to answer several questionnaires to measure the subjective level of presence they experienced. As in the fMRI scans, the questionnaires the subjects had to fulfill were SUS questionnaires (Usoh et al., 2000), which evaluate the level of presence that they felt during each task. Subjects had to complete 3 questionnaires, one for each task, all containing the same questions (see Appendix 4).

3.2.3.1.3 EEG Procedures

All the subjects were scanned in a laboratory inside the LabHuman group (I3BH Institute, UPV, Valencia, Spain). For the navigation, they used a common joystick. The DS group saw the environments in a common PC desktop screen located over a desk. The PW group viewed the environments in a 6m wide power wall screen located in front of them (separation of 3m). They were also sat in front of a desk, where the joystick was placed. All the subjects were instructed to sit comfortably and try not to move. If they wore glasses, they were asked to carry them instead of lenses, to avoid the greater dry of the eyes. They were also asked to try not to blink too much. The

researchers that conducted the studies were sit behind the subject (so he were not distracted by their presence) with the computer where the EEG signals were captured. Regarding the EEG device, it was a low-resolution multichannel wireless portable Emotiv EPOC headset, with 14 data-collecting electrodes and 2 reference ones. The handset transmits wirelessly the EEG data to the computer.

Figure 3.19 Image of a subject in front of the power wall wearing the Emotiv EPOC

All the subjects were recruited by announces at the University or the word-of-mouth. They were students of the UPV or members of the staff. When they arrived, they were taken to an auxiliary room where they were introduced to the tasks they would have to perform. All the experiment was explained to them and they passed through a training session where they practiced the tasks and the joystick movement (as well as the subjects did in the fMRI study). They also fulfilled a questionnaire to assure their hand dominance. Once they had understood everything and signed the informed consent, they were conducted to the room where the scans took place. There, they were instructed to sit behind the desk and the EEG device was placed. Once everything was all right, the lights were turned off and the scan began.

For placing the EEG headset, the electrodes were dampened with cleansing solution and the device was placed over the head, leaving a distance of 3cm between the eyebrows and the frontopolar electrodes. Then the rest of the electrodes were checked to assure they were in the correct position and the headset was turned on, transmitting the electrical signals of the brain wirelessly to the computer. If everything was ok, the 14 signals were received correctly, and the software in the computer will display all the electrodes in green color. The simplicity and low number of electrodes of this device makes it easy to place, taking just a few minutes to adjust everything.

3.2.3.1.4 Data Analysis

3.2.3.1.4.1 Questionnaire Analysis

Similarly to what was done in the fMRI study, SPSS 17.0 (IBM Corporation, Somers, New York, USA) was used for the analysis of the questionnaire results. The responses to the six questions and the SUS mean (mean of those six responses) for the three experimental conditions (photographs, video and navigation) were considered for the analysis. A non-parametric Friedman Test was applied to compare SUS responses (dependent variables: questions 1-6 and SUS mean) for the different experimental conditions: photographs, video and navigation. The post-hoc tests were made with a Wilcoxon Signed-Rank test with Bonferroni correction.

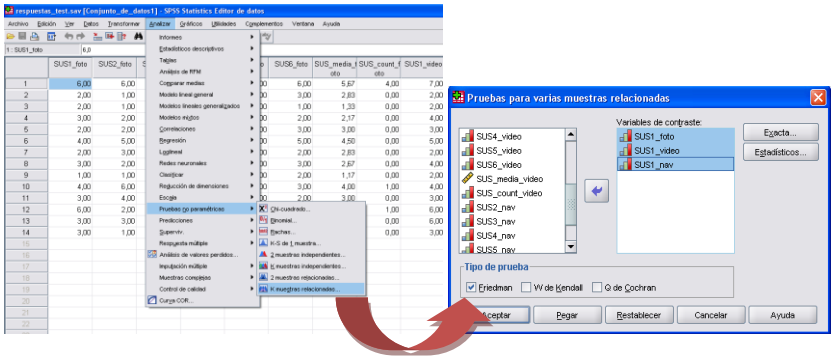


Figure 3.20 Captures of the SPSS

3.2.3.1.4.2 EEG Analysis

The preprocessing of the signals was made by means of the EEGLAB program (Delorme and Makeig, 2004), launched with Matlab Version 7.1 (MathWorks, Natick, Massachusetts, USA). The data were imported from EDF and the sensors from which information was wanted were selected.

The baseline was removed and all recorded EEG epochs were checked for artifacts. First of all, data were digitally filtered using a linear FIR band pass filter (0.5-45 Hz). Then, the electrooculographic (EOG) artifacts were removed applying Blind Source Separation (BSS), using a window length of 10s, with 5s between windows. The electromyographic (EMG) artifacts were removed using also the BSS method.

For the analysis of the activated brain areas, the sLORETA tool was used (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994, 1999; Frei et al., 2001). The whole brain was analyzed using voxel-wise t-tests for examining the navigation vs. video and navigation vs. photographs conditions in the six frequency bands. Moreover, the same voxel-wise t-tests were used for comparing between the navigation conditions for the two groups (DS vs. PW) in the six frequency bands.

3.2.3.2 Results

3.2.3.2.1 Questionnaire Results

The answers to the SUS questionnaire showed variations between the different experimental conditions. Mean values in each condition are shown in Table 3.12. Results from applying the non-parametric Friedman Test showed that there were significant differences between the three experimental conditions for all the questions and the SUS mean (results can be observed in Table 3.12, columns 5 and 6). If observed the results for each question, there can be seen that for the DS group, the greatest Chi-square value ($\chi 2 = 16.222$, $p < 0.001$) was observed for questions 1 and SUS mean; while for the PW

group, the greatest Chi-square value ($\chi 2 = 13.556$, $p < 0.001$) was observed for questions 1 and 3.

		Photograph	Video	Navigation	χ^2	P
SUS question 1: feeling of "being there"	DS	1.89±0.35	3.11±0.31	4.89±0.39	16.222	0.000
	PW	2.90±0.33	3.80±0.26	4.80±0.41	13.556	0.001
SUS question 2: feeling that the room is real	DS	2.22±0.43	3.00±0.33	4.78±0.40	12.400	0.002
	PW	2.40±0.23	3.70±0.35	4.30±0.39	12.286	0.002
SUS question 3: how real do you remember the room?	DS	1.56±0.24	2.67±0.24	4.11±0.39	15.548	0.000
	PW	2.20±0.34	3.40±0.32	4.50±0.39	13.556	0.001
SUS question 4: feeling of being inside the room or observing it	DS	2.00±0.37	2.89±0.51	4.78±0.49	14.813	0.001
	PW	2.50±0.28	3.40±0.28	4.80±0.44	12.600	0.002
SUS question 5: memory of the room as similar to being in other places	DS	2.89±0.42	2.89±0.39	3.78±0.49	10.800	0.005
	PW	2.90±0.46	3.70±0.32	4.70±0.39	9.680	0.008
SUS question 6: did you think you were really in the room?	DS	2.33±0.37	3.22±0.28	4.78±0.47	9.800	0.007
	PW	2.60±0.48	3.40±0.36	4.40±0.48	10.000	0.007
SUS mean	DS	2.15±0.28	2.96±0.24	4.52±0.35	16.222	0.000
	PW	2.58±0.27	3.57±0.23	4.59±0.36	12.839	0.002

Table 3.12 SUS responses to questionnaires for each task (mean score and standard error of the mean) and results of the Friedman Test for each question and the mean score

Post-hoc analyses based on Wilcoxon Signed-Rank Tests were conducted on the SUS mean results with Bonferroni correction, resulting in a significance level set at $p < 0.0167$. For the DS group, there were no significant differences between the photograph and video tasks ($Z=2.082$, $p=0.037>0.0167$), but there were for the comparisons navigation vs. video ($Z=2.668$, $p=0.008<0.0167$) and navigation vs. photograph ($Z=2.668$, $p=0.008<0.0167$). For the PW group, there were no significant differences between the photograph and the video tasks ($Z =2.380$, $p = 0.017 > 0.0167$) and between the photographs and navigation tasks ($Z=2.366$, $p=0.018>0.0167$). However, there was a statistically significant increment in the SUS

mean in the navigation condition compared with the video condition (Z =2.521, p = 0.012 < 0.0167). Those results are contained in Table 3.13. Finally, it should be mentioned that no significant difference was found for the questionnaire answers between groups (DS vs. PW) for any of the three experimental conditions.

	DS		PW	
SUS mean	Z	P	Z	P
Navigation>Video	2.668	0.008	2.521	0.012
Navigation>Photographs	2.668	0.008	2.366	0.018
Video>Photographs	2.082	0.037	2.380	0.017

Table 3.13 Results of the Wilcoxon Signed-Rank Test for the comparison of the SUS mean results between experimental conditions

3.2.3.2.2 EEG Results

For the DS group, the comparison between the Navigation and Video conditions using voxel-wise t-test for all the frequency bands revealed significant differences in the Alpha-band (8-12 Hz) and Theta-band (4-7 Hz), for p<0.05. Alpha and Theta band power was decreased in the Navigation condition in the right Insula (BA 13), indicating increased activity in this region during the free navigation task.

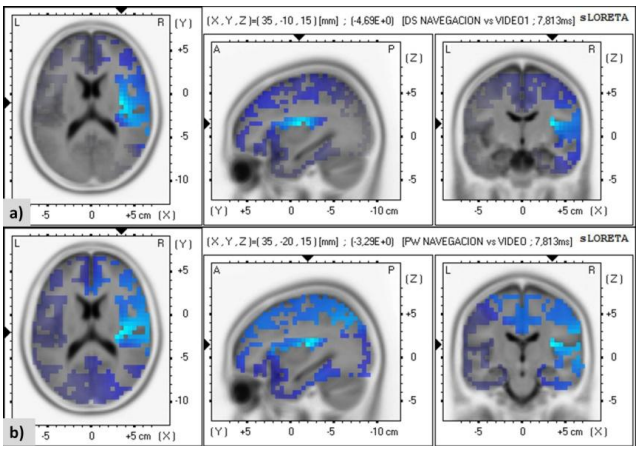


Figure 3.21 Results for the navigation>video contrast for both experimental groups. Captures of sLORETA activation for the navigation>video contrast in the Theta band for: a) DS group, b) PW group

For the PW group, the same comparison between the Navigation and Video conditions, again using voxel-wise t-test for all frequency

bands, revealed significant differences in the Theta-band (4-7 Hz), for p<0.05. Theta band power was decreased in the Navigation condition in the right Insula (BA 13), indicating increased activity in this region during the free navigation task. There has also been found a trend (p<0.1) to increased activity in the Insula (BA 13) and in the Parietal Lobe (BA 40) for the Alpha-band. A comparison between the results for the navigation>video contrast in the theta band can be seen in Figure 3.21. All the results for this contrast are contained in Table 3.14.

Group	Brain Area	Band	Hemisphere	p
DS	Sub-Lobar, Insula (BA13)	Theta	Right	<0.05
DS	Sub-Lobar, Insula (BA13)	Alpha	Right	<0.05
PW	Sub-Lobar, Insula (BA13)	Theta	Right	<0.05
PW	Parietal Lobe, Inferior Parietal Lobule (BA40, 39, 7)	Alpha	Right	<0.1
PW	Parietal Lobe, Precuneus (BA19)	Alpha	Right	<0.1
PW	Parietal Lobe, Angular Gyrus (BA39)	Alpha	Right	<0.1
PW	Parietal Lobe, Superior Parietal Lobule (BA7)	Alpha	Right	<0.1
PW	Sub-Lobar, Insula (BA13)	Alpha	Right	<0.1

Table 3.14 Comparison of the results for the DS and PW groups for the navigation>video contrast

Regarding the results for the comparison between the conditions of Navigation and Photographs, no significant results were found for any group, but several areas with tendency to significance were found in the PW group. For the Alpha band, the DS group presented a trend to activation for p>0.1 in several frontal and temporal areas, as well as in the parahippocampal gyrus. For the PW group, also in the Alpha band, it was found the major significance result in the Uncus of the parahippocampal gyrus, part of the Limbic Lobe; and tendency to significance in other areas of the temporal and frontal areas. The complete results for this contrast are contained in Table 3.15. The

comparison between the video and photographs conditions did not give any significant results.

Group	Brain Area	Band	Hemisphere	p
DS	Sub-Lobar, Insula (BA13)	Alpha	Right	>0.1
DS	Frontal Lobe, Subcallosal Gyrus (BA34, 13)	Alpha	Right	>0.1
DS	Frontal Lobe, Inferior Frontal Gyrus (BA47, 13, 11)	Alpha	Right	>0.1
DS	Frontal Lobe, Orbital Gyrus (BA47)	Alpha	Right	>0.1
DS	Frontal Lobe, Middle Frontal Gyrus (BA11)	Alpha	Right	>0.1
DS	Frontal Lobe, Medial Frontal Gyrus (BA25)	Alpha	Right	>0.1
DS	Limbic Lobe, Uncus (BA20, 28, 34)	Alpha	Right	>0.1
DS	Limbic Lobe, Parahippocampal Gyrus (BA36, 35, 34, 28, 27)	Alpha	Right	>0.1
DS	Temporal Lobe, Fusiform Gyrus (BA20)	Alpha	Right	>0.1
DS	Temporal Lobe, Inferior Temporal Gyrus (BA20)	Alpha	Right	>0.1
DS	Temporal Lobe, Superior Temporal Gyrus (BA38)	Alpha	Right	>0.1
DS	Occipital Lobe, Lingual Gyrus (BA18)	Alpha	Left	>0.1
PW	Limbic Lobe, Uncus (BA28)	Alpha	Right	>0.05
PW	Limbic Lobe, Uncus (BA28, 36, 34, 20, 38)	Alpha	Right	<0.1
PW	Limbic Lobe, Parahippocampal Gyrus (BA34, 35, 28)	Alpha	Right	<0.1
PW	Temporal Lobe, Superior Temporal Gyrus (BA38)	Alpha	Right	<0.1
PW	Temporal Lobe, Inferior Temporal Gyrus (BA20)	Alpha	Right	<0.1
PW	Temporal Lobe, Middle Temporal Gyrus (BA38)	Alpha	Right	<0.1
PW	Frontal Lobe, Subcallosal Gyrus (BA34)	Alpha	Right	<0.1
PW	Frontal Lobe, Inferior Frontal Gyrus (BA47)	Alpha	Right	<0.1

Table 3.15 Comparison of the results for the DS and PW groups for the navigation>photographs contrast

Finally, using voxel-wise t-test for all frequency bands, significant differences were found when comparing the Navigation condition between both experimental groups (DS vs. PW) for the Theta and Alpha bands. For the Theta band, activations were found in the insula, the parahippocampal gyrus and several areas from the temporal and frontal lobes in the left hemisphere; and in the subcallosal gyrus of the frontal lobe in the right hemisphere. For the Alpha band, similar activations were found in the Insula, parahippocampal gyrus and several temporal and frontal areas, all of them in the left hemisphere of the brain. A comparison for the navigation condition between the brain activations for DS and PW groups is shown in Figure 3.22. The complete results are contained in Table 3.16.

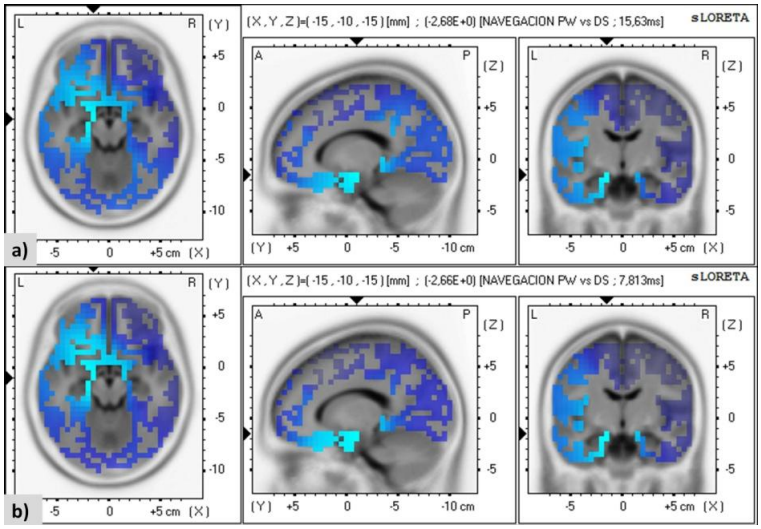


Figure 3.22 Results for the navigation condition between groups. Captures of sLORETA activation for the navigation condition in the DS vs. PW comparison for: a) Alpha band, b) Theta band

Brain Area	Band	Hemisphere	p
Sub-Lobar, Insula (BA13)	Theta	Left	<0.05
Sub-Lobar, Extra-Nuclear (BA13, 47)	Theta	Left	<0.05
Limbic Lobe, Uncus (BA34, 28, 36, 38, 20)	Theta	Left	<0.05
Limbic Lobe, Parahippocampal Gyrus (BA28, 34, 35, 36)	Theta	Left	<0.05
Temporal Lobe, Inferior Temporal Gyrus (BA13)	Theta	Left	<0.05
Temporal Lobe, Superior Temporal Gyrus (BA38)	Theta	Left	<0.05
Frontal Lobe, Subcallosal Gyrus (BA34, 13, 25)	Theta	Left	<0.05
Frontal Lobe, Inferior Frontal Gyrus (BA47, 13, 11)	Theta	Left	<0.05
Frontal Lobe, Orbital Gyrus (BA47)	Theta	Left	<0.05
Frontal Lobe, Middle Frontal Gyrus (BA11)	Theta	Left	<0.05
Frontal Lobe, Medial Frontal Gyrus (BA25)	Theta	Left	<0.05
Frontal Lobe, Rectal Gyrus (BA11)	Theta	Left	<0.05
Frontal Lobe, Subcallosal Gyrus (BA25)	Theta	Right	<0.05
Sub-Lobar, Insula (BA13)	Alpha	Left	<0.05
Sub-Lobar, Extra-Nuclear (BA13)	Alpha	Left	<0.05
Limbic Lobe, Uncus (BA28, 34)	Alpha	Left	<0.05
Limbic Lobe, Parahippocampal Gyrus (BA28, 34, 35, 27)	Alpha	Left	<0.05
Temporal Lobe, Superior Temporal Gyrus (BA38)	Alpha	Left	<0.05
Frontal Lobe, Subcallosal Gyrus (BA34)	Alpha	Left	<0.05
Frontal Lobe, Medial Frontal Gyrus (BA25)	Alpha	Left	<0.05
Frontal Lobe, Inferior Frontal Gyrus (BA47, 13)	Alpha	Left	<0.05

Table 3.16 Comparison of the results for the navigation condition between DS and PW groups

3.2.3.3 Discussion of the results

In the present study, an Emotiv EPOC headset was used to evaluate the level of presence experienced while navigating in a virtual environment, in comparison with two other experimental conditions (view of photographs and videos of the virtual environment). Several theories have related the sense of presence with the capability "to do" inside the virtual environment, so a higher immersive and commanding task should enhance the sense of presence. The subjects were divided into two groups, depending on the screen used to display the environments. The first group performed the task in a

common PC desktop screen (DS) while the second group performed it in a power wall screen (PW). According to the literature (Ijsselsteijn et al., 2001; Slater et al., 1995; Kober et al., 2012), a larger and more realistic screen should enhance a major sense of "being there" in the subject; so higher levels of presence are expected in the PW group than in the DS group. As Kober et al. (2012) pointed out, "the screen size enhances the psychological impact of motion stimuli, because a larger portion of peripheral vision is being stimulated". So, in conclusion, the signals will be analyzed looking for differences in the sense of presence due to two conditions: the possibility of "doing" inside the virtual environment (comparison between experimental conditions) and the influence of the kind of screen used for the display of the environments (comparison between groups, DS vs. PW).

First, the results related to the "to do" theory will be analyzed. Both for the DS and PW groups, it was found activation in the insula while comparing the navigation and video conditions. What is more, significant differences were also found in the questionnaire results (Wilcoxon Signed-Rank test) between the SUS mean values for both conditions; so the greater sense of presence is experienced during the navigation condition.

The insula is related to emotion and regulation of the body's homeostasis, which includes among other functions self-awareness or the sense of agency and body ownership (Karnath et al., 2005). The sense of body ownership is the property which allows you to discriminate your own body and perceptions; forming the "body schema" which guides your behavior (Haans and IJsselsteijn, 2012). Recent works (Dodds et al., 2011) have found evidence that the right insula may be activated by a combination of attentional and response control demands, playing a role in the processing of sensory stimuli that are relevant to the current goals. While navigating in a VE, you make decisions all the time, based on the evaluation of the sensory stimuli that guides our behavior in the VE. The findings of this work

suggest that the insula may play a key role in guiding behavior in the virtual environment based on the presented stimuli and the sense of presence. Moreover, according to Sjölie (2012), attention and behavior are essential to develop the sense of presence, increasing the precision in the predictions about the environment and the synchronization with it, and avoiding prediction errors from sources outside the VE.

In the study of Baumgartner et al. (2006), they also found activation in the insula while evaluating the sense of presence experienced while watching a video of high and low arousing VEs using EEG. The subjects under study were divided in two groups, one of children and another of adolescents. They found activation in the insula for both groups while comparing the high arousal condition with the control one. As they concluded, the insula "receives homeostatic afferents from several modalities, including temperature, pain, proprioception, and the viscera and, thus, is involved in the mapping of body related sensations".

Regarding the study of Kober and Neuper (2012) using event-related brain potentials of the EEG to indicate the level of presence experienced in a VE, they found an increased presence experience associated with a decrease in the late negative slow wave amplitude, related to the central stimulus processing and the allocation of attentional resources. In concordance with what has already been exposed, they found a direct relation between the attention to the VR and the increase in the sense of presence.

In another previous study about presence with EEG (Kober et al., 2012), they compared the presence-related activations while navigating through a VR world in two conditions: visualization in a Desktop-VR-condition and in a Single-Wall-VR-condition. They found a more intense presence experience in the Single-Wall-VR-condition than in the Desktop-VR-condition, accompanied by an increased parietal TRPD in the Alpha band. Moreover, they found a stronger functional connectivity between the frontal and parietal regions

during the Desktop-VR-condition. The activation in the parietal area is close to some of the results presented here (it was also found activation in this area for the PW group when comparing between the navigation and video conditions).

In the previous study conducted using fMRI to measure presence while navigating in the same virtual environments (Clemente et al., in press), activation in the insula (among other areas) was also found when comparing the conditions of navigation and video. Moreover, the results showed a parametric increase in the right insula activation among the three experimental conditions.

Apart from that result, for the navigation>video comparison the PW group also showed a tendency to significance for the Alpha band in the right parietal lobe. More precisely activations were found in the superior and inferior parietal lobules, precuneus and the angular gyrus. The superior parietal lobule is mainly involved with spatial orientation (Karnath, 1997; Corbetta et al., 1995), which makes sense due to the increased necessity of orientation while navigating than while viewing a video. The inferior parietal lobule has been involved in the interpretation of sensory information (Radua et al., 2010), which the subject receives in a higher amount while navigating. The precuneus has been widely related to presence and navigation, being involved in directing attention in space (Cavanna and Trimble, 2006). At last, the result of the angular gyrus is quite interesting. This area is related to the sense of self-awareness and the developing of Out-of-body experiences (Arzy et al., 2006). Several studies have been conducted to study this phenomenon (Blanke et al., 2002; Arzy et al., 2006), concluding that it is attributed to a discrepancy between the actual position of the body and the mind's perceived location of the body. This statement agrees with the theory of presence.

Regarding the results for the navigation vs. photographs comparison, it was only found significant results for the alpha band in the right uncus (part of the limbic lobe) for the PW group. This is an important result, because this area plays an important role in the generation of

the sense of presence. The uncus is the extreme area of the parahippocampal gyrus. The activation of the parahippocampal gyrus is related to memory encoding and retrieval (Epstein and Kanwisher, 1998). A subsection of this area is the parahippocampal place area (PPA), corresponding to the BA35, which plays a role in the encoding and recognition of scenes over faces and objects. That means that this area is activated while the subject is seeing a topographical scene, as it can be a room (Epstein and Kanwisher, 1998; Aguirre et al., 1996). The activation of this area during the navigation condition and not during the view of photographs means that there is a higher identification of place while navigating through a room than when you only see a picture of it. This area has been described as related to the view of real places and its activation while viewing a virtual place confirms that the subject feels the experience as real.

Apart from the limbic lobe, it was also found tendency to activation in the temporal and frontal areas. Regarding the activations in the temporal areas, the inferior temporal gyrus is normally related to the visual processing associated to complex objects and shape (Chao et al., 1999), while the superior temporal gyrus is more related to the perception of emotions (Radua et al., 2010). Although the function of the middle temporal gyrus is unknown, it has been connected with several functions, such as the view of distance (De Luca et al., 2006).

Regarding the activations in the frontal areas, the subcallosal gyrus is related to the parahippocampal activation, and both areas work together in the periarcheocortex; while the BA47 of the inferior frontal gyrus has been implicated in the processing of syntax in oral, sign and musical languages (Levitin and Menon, 2003).

Finally, the results from the comparison between both experimental groups for the navigation condition will be discussed. Here activations were found in some of the areas related before, although this time on the left side of the brain. The only significant difference obtained in the right side was in the subcallosal gyrus of the frontal lobe for the Theta band (and for both Theta and Alpha bands in the

left side), related to the parahippocampal activation, which as aforementioned plays a role in the encoding and recognition of scenes over faces and objects (Epstein and Kanwisher, 1998; Aguirre et al., 1996). The parahippocampal gyrus also presents a significant activation for the left hemisphere in both Theta and Alpha bands. There is a close activation in the superior temporal gyrus, related to the perception of emotions (Radua et al., 2010).

Another remarkable result was the activation of the left insula for the Theta and Alpha bands, involved in self-awareness or the sense of agency and body ownership (Karnath et al., 2005). Apart from these areas, other significant activations were found in different parts of the frontal lobe.

Regarding the questionnaire results, they confirmed that a higher level of presence was induced during the free navigation than during the automatic navigation and the photographs conditions. Specifically, the Friedman Test showed significant differences between the experimental conditions for all the questions and the SUS mean with higher presence values for the navigation condition. Moreover, the Wilcoxon Test showed the existence of significant differences between the navigation and video conditions for both groups (DS and PW). On the other hand, there were no significant differences for each condition between groups. Because each subject only performed the task in one kind of screen, they were not able to compare the changes between the DS and the PW. This is in accordance with the lack of sensibility of the subjective questionnaires, being unable to differentiate between groups, field where the EEG was successful. The answers given to the questionnaires were subjective and relative to what they had experienced, that is to say, they scored the sense of presence in the navigation condition in comparison with the sense experienced in the other two conditions; and not being able to compare between screens, the DS group scored the experience similarly to how the PW group did. However, those changes in the sense of presence were

detected by the EEG signals, finding clear significant differences between groups.

In this part of the presence study, one important goal was to show the usability of the Emotiv EPOC headset in presence research. It has been used to measure brain activations related to presence in different experimental conditions, obtaining similar results to those obtained in previous works. Moreover, it was a goal of the study to analyze whether a bigger and more immersive screen would enhance a sense of presence and show differences in brain activation with less immersive configurations, as postulated by Kober et al. (2012). The EEG results showed significant differences while comparing both conditions in areas related to presence (such as the aforementioned insula). However, those results were not obtained with the questionnaires, which may be explained by the greater sensibility of the EEG measures.

However, the main goal was to obtain using EEG the brain areas related to the sense of presence in order to compare them with those obtained in the previous fMRI study (Clemente et al., in press) and decide which neuroimaging technique is better for the objectives of this Thesis. In the fMRI, as mentioned in the previous section (Section 3.2.2), activations were found in the insula and the parietal lobe (between others) related to a greater sense of presence while navigating in a virtual environment, result that have been also obtained in this work. In the following section (Section 3.2.4) this comparison will be described in detail.

3.2.4 Comparison of the fMRI and EEG presence studies

Once both the fMRI and the EEG presence studies have been presented, it will be done a comparison of the results obtained in each one, and then some overall conclusions will be extracted. First, the comparison of the questionnaire results will be made. Then, the brain activations from both researches will be contrasted.

3.2.4.1 Methods

The results from the SUS questionnaires of the fMRI and EEG studies have been compared. For this comparison, there are three groups of contrast: the fMRI group, consisting in 14 subjects; the EEG DS group, formed by 9 subjects; and the EG PW group, composed by 10 subjects. The results to compare belong to the three experimental conditions: navigation, video and photographs. For this it has been applied a repeated measures ANOVA to evaluate the influence on the dependent variable (SUS mean) of the within-subjects factor (experimental condition: photographs, video or navigation) and the between-subjects factor (group: fMRI, EEG DS or EEG PW). The homocedasticy was evaluated with the Levene statistic.

3.2.4.2 Comparison of the questionnaire results

As it has been already found separately for each study, there were significant differences between the experimental conditions (photographs, video and navigation) when comparing the three groups ($F(1,31)=46.328$, $p<0.005$). Moreover, as expected, there were no significant differences between the different groups ($F(1,31)=0.393$, $p=0.678$). That means that the presence results do not vary significantly with the neuroimaging technique applied. The subjects subjectively felt equally real the virtual experiences, independently of if they were laid inside a fMRI scan or if they were sit in a more comfortable chair with the screen in front of them; what is more, there were also no significant differences regarding the size of the screen used. On the other side, there were significant differences for the interaction factor between the experimental condition and the monitoring technique used ($F(1,31)=3.356$, $p=0.036<0.05$). A power analysis using the G*power3 program (Faul et al., 2007) showed that a total sample of 42 subjects would have been required to obtain the recommended 80% power in a t test comparison between fMRI and EEG, with alpha set at 0.05 and Cohen's d at 0.8 (large effect size).

Regarding the interaction between groups and experimental conditions two-by-two, the results obtained are shown in the following table (Table 3.17).

F(1,31)	Photographs	Video	Navigation
EEG PW vs DS	0.434, p=1.000	0.604, p=0.756	0.068, p=1.000
fMRI vs EEG DS	0.719, p=0.331	0.217, p=1.000	-0.743, p=0.592
fMRI vs EEG PW	0.285, p=1.000	-0.387, p=1.000	-0.812, p=0.443

F(1,31)	video vs. photographs	navigation vs. photographs	Navigation vs. video
EEG DS	0.812, p=0.024	2.367, p<0.005	1.554, p<0.005
EEG PW	0.982, p=0.003	2.001, p<0.005	1.019, p=0.001
fMRI	0.310, p=0.562	0.904, p=0.061	0.595, p=0.021

Table 3.17 Comparison of the results for the interactions between the groups and the experimental conditions

As can be seen in Table 3.17, there were no significant differences between groups for the three experimental conditions (as it was expected). However, there were significant differences for each group separately for the comparisons between experimental conditions (unless in the case of the comparisons navigation>photographs and video > photographs for the fMRI data, result in accordance to what we saw in the fMRI study).

3.2.4.3 Comparison of the brain activations

When comparing the brain activations between the fMRI and EEG results, it is found an added difficulty in the different spatial resolution of both techniques, which makes the fMRI results more precise and located, and the EEG results more spread and imprecise (it must be remembered that this is because the EEG does not measure brain activations directly but approximates it by means of the sLORETA tool). However, some overall comparisons can still be made.

First of all, let's focus on the principal contrast of both results: the "navigation>video" contrast. There is only one cerebral region that is activated in the three experimental groups (fMRI, EEG DS and EEG PW), however, this area is of principal interest in the study of presence: the Insula. The right Insula (BA 13) is significantly activated for the fMRI groups as well as for both EEG groups in the alpha and theta bands (which are the areas commonly related to in the presence studies). As aforementioned, this area is related to the sense of self-awareness and agency of body ownership (Karnath et al., 2005). In both discussions of the corresponding studies it was justified the direct relation of this area with the sense of presence. Moreover, most of previous works in the matter have obtained this same activation.

Apart from the Insula, the EEG DS group did not get any other significant result, but for the EEG PW there was activation in several areas of the Parietal lobe. For the fMRI group activation was found in the postcentral parietal lobe. Although these activations are not exactly located on the same place, they are close and (considering again the low accuracy of the EEG) may refer to the same brain function. And what is more important, those exact two activations were the same that in the fMRI study showed a pattern of linear increase with the sense of presence between experimental conditions.

Secondly, regarding the "navigation>photographs" contrast, there were some equivalent activations in the frontal and occipital (lingual gyrus) lobes. However, for this contrast it must be remembered that the significance of the activations for the EEG studies was not good, so those results are not to take in account thoroughly.

Finally, for the "video>photographs" contrast in the EEG studies there were not found significant results neither; thing that makes sense due to the lower resolution of the device and the little sense of presence stimulated by those two conditions.

3.2.5 Overall conclusions of the presence study

So, in conclusion, the main comparisons between the two neuroimaging devices will be done for the "navigation>video" contrast, that is the one which showed significant results for both EEG groups. Moreover, this contrast, as remarked before, is the one really interesting for the purposes of this study, because it was the one that measured the differences in the sense of presence between two really involving conditions (automatic vs. free navigation).

As pointed out in the previous section, for both EEG groups it was found significant activation for the alpha and theta bands in the Insula, the same result found for the fMRI group. Moreover, this and the Parietal lobe (also activated for the EEG PW group) were the areas which activation increased between experimental conditions. So both neuroimaging techniques obtained similar brain activation result. As remarked in Section 3.2.4.2, for the questionnaire results there were no significant differences in the sense of presence reported between groups, although it was between experimental conditions. The sample size was not enough to obtain the required statistical power for the comparison between groups, but both studies' questionnaire results showed similar patterns of increase of the sense of presence with the experimental experience (see Figure 3.23). For both studies there were significant differences between conditions and in both the value of the SUS mean for the navigation condition was higher than 3.7. So, in conclusion, with both techniques it was possible to stimulate the sense of presence, which was not significantly influenced by the neuroimaging technique chosen.

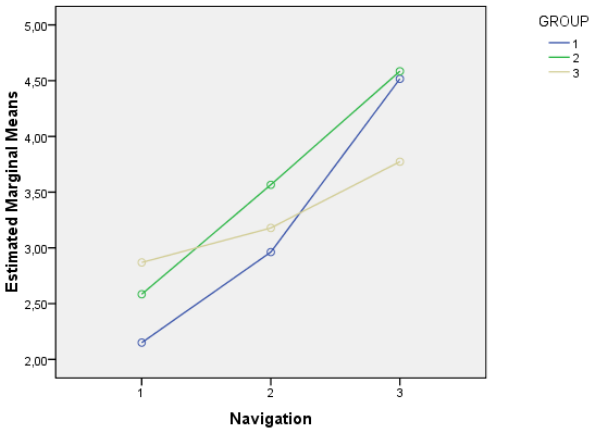


Figure 3.23 Comparison of the patterns of increase of the sense of presence for the questionnaire results (SUS mean), where EEG DS is group 1, EEG PW is group 2 and fMRI is group 3

That means that the virtual experience was strong enough to elicit the sense of presence, even while the subject was laid inside a fMRI scanner, with all the noise and uncomfortable features that this implies. This encouraged the continuation of the second part of the study (the assessment of subjects before and after undergoing a psychological treatment), knowing that the environment was felt as real enough to stimulate the brain areas required (in this case, those related to fear).

Once checked that both neuroimaging techniques were able to measure brain areas with similar results, a choice had to be made about which one to employ for the next study. The chosen one was the fMRI due to its better spatial resolution, because it is more interesting for the purposes of this study the precision of the brain activity locations than the temporal evolution or less intrusion of the device.

In the next chapter (Section 4) the results for the study of the changes in the brain areas activated before and after undergoing a psychological treatment with fMRI will be presented.

4 Assessment of a treatment: Small Animals' Phobia

At this point of the Thesis, the two questions that arose when outlining the principles of the study have already been answered. On the one hand, the stimulation of the sense of presence in the subjects during the virtual experience was checked, both by means of the two neuroimaging techniques proposed and by the use of subjective questionnaires. On the other hand, no significant differences have been found between the questionnaire answers given by the subjects from the three groups (fMRI, EEG DS and EEG PW), finding equivalent brain activations with both neuroimaging techniques (although with less spatial accuracy in the EEG results than in the fMRI images), what means that the intrusion of the scan does not affect to the effectiveness of the environments. According to this, it has been resolved that the best neuroimaging technique for the assessment of a psychological treatment in the context of the present work would be the fMRI, due to its better spatial resolution, not based on an approximation done with a standardized tool (the sLORETA in the EEG study) but on real functional data.

So, once it has been stated that the subjects feel present while navigating through the virtual environment and once it has been decided the best tool to scan the brain, everything is ready to study how neuroimaging combined with VR can help in the assessment of the patient's response to a psychological treatment, analyzing his state before and after undergoing the therapy. For this, the research has been focused on a specific disorder: the small animals' phobia; and the brain activations related to the fear and anxiety the subject feels while exposed to phobic stimuli will be measured.

Phobias are one of the most spread and common disorders of the modern life, affecting one person in 10 at some point of their lives (American Psychiatric Association, 2000; Magee et al., 1996; Kessler et al., 2005). More specifically, small animals' phobia is one of the most disabling ones, due to the possibility of facing the animal that is

the focus of the phobia in daily life. In fact, 40% of specific phobias belong to the category of small animals, including bugs, mice, snakes and bats (Chapman, 1997).

In order to evaluate the state and evolution of the phobia, many studies have been conducted using brain imaging techniques, such as fMRI, PET or EEG. Until now, most of those studies have used photographs or videos of real animals as stimulus to provoke the reaction of the subject. However, the advantages of Virtual Reality have not been used to explore the brain activations while navigating through a virtual environment that would represent a more realistic and interactive representation of the phobic situation. Until now, the VR has been used for the treatment of the phobia, but not for the assessment of the disorder while analyzing the brain using neuroimaging. In this section of the PhD, fMRI will be used to evaluate the brain activations related to the small animals' phobia. Moreover, the phobic subjects were treated with a psychological treatment for the phobia, after which the fMRI scan was repeated. Then the activations before and after the treatment will be compared to assure that the brain areas related to the phobia stopped being activated after it.

4.1 Theoretical aspects of phobias

When you are in danger, you experiment a feeling of fear that awares you and keeps you in an alert state. This fear helps you to realize the importance of the situation, like a mental advisory of the existing risk. However, in the case of phobias, this fear is awakened by an unreal situation, not as threatening as it is thought by the subject. It can be described as "an abnormally fearful response to a danger that is imagined or is irrationally exaggerated" (American Psychiatric Association, 2000).

The phobia can be stimulated by different kinds of stimulus, such as animals (spiders, snakes, birds…), activities (like flying) or social situations (e.g. agoraphobia, social phobia…). This Thesis is focused

on small animals' phobia, a category that involves mice, bugs, snakes and bats (Chapman, 1997).

This phobia consists in an irrational fear before any possible contact with the animal in question. This fear is joined to a continuous state of anxiety before the possibility of finding it, a repulsion response before any representation of it and a defensive reaction in case of contact. It must also be considered that there are no limitations in phobias by age, gender, geographic location or way of life.

Talking about statistics, phobia affects approximately one person in 23, which is nearly the 4.25% of the world's population. Just in the US, it is estimated that about 10-11% of the population experiences specific phobia at some point of their lives (American Psychiatric Association, 2000). Regarding the way of acquisition of the phobia Ost and Hugdahl (1981) found that the majority of phobic subjects reported acquiring their fear via conditioning (58%), and between the rest, it was because of an external instruction (10%), in a vicarious way (15%); or they just couldn't remember (10%).

Specific phobias tend to be considered less important than other psychological problems by clinics and sufferers. In fact, patients of specific phobias are the less frequent in seeking treatment. This is normally because the fear associated with specific phobias is limited to the phobic stimuli, and does not cause pervasive anxiety to the subject outside the phobic situation (Hood and Anthony, 2012). However, individuals with specific phobia are sufferers of serious life impairments, such as the interference of the fear with their social lives, reduced productivity at work or failure to seek medical care. This eventually can lead to a complex symptom profile, including physiological symptoms, extensive coping and avoidance behaviors, and unhelpful or distorted cognitions (Hood and Anthony, 2012).

Specific phobias are divided in four groups (American Psychiatric Association, 2000): animal type (where the small animal's phobia would be included, together with dogs, snakes, mice or birds),

natural environment type (such as heights, storms, water…), blood-injection-injury type (as the group name points out, fear to the vision of blood, receiving an injection or to pain) and situation type (e.g., airplanes, elevators, enclosed places). The DSM-IV also describes a category called others, which includes other types of specific phobias such as fear of choking, vomiting, or contracting an illness; or, in children, fear of loud sounds or costumed characters. The diagnostic criteria (DSM-IV) for 300.29 specific phobia can be seen in Appendix 5.

For the assessment of the specific phobia, normally three basic procedures are developed: a clinical interview, the behavioral assessment of the patient and the fulfillment of standard self-reported scales (Grös and Antony, 2006). The clinical interview consists in the assessment of the subject's phobia and the gravity of this phobia. During the interview, the patient is asked about his fears (etiology, origin, course…), the kind of reactions he experiments when exposed to it (panic attacks, fainting…), his beliefs about the object of the phobia (predictions, belief in unreal responses from the phobic situation, such as thinking a spider is going to attack you…), avoidance responses (e.g. places you do not go because you think the feared animal will be there), variables that increases his fear (for example, the weather in cases of driving phobia),… In the same interview, the patient is confronted to the phobic stimuli or situation (behavioral assessment), so the interviewer can assess the presence of the phobia and the level of discomfort caused in the subject. There are some models of semistructured interviews which help the clinician during the process, such as the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV; Brown et al., 1994), the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 2007) or the Mini International Neuropsychatric Interview (MINI; Sheehan et al., 1998). For example, in the experimental study exposed in this chapter, the adult version of the ADIS-IV, which consists in a series of questions to rate between 0 (none) and 8 (very severe) fear, was used. This scale can be seen in Appendix 6.

For the behavioral assessment, tests such as the Behavioral Approach Test (BAT) are used. It involves measuring the patient's responses during the exposure to the phobic object or situation (distance to the stimuli, rating of the fear experienced…). It is normally conducted during the clinical interview, and gives the clinician a more accurate and objective idea of the state of the subject. In some occasions, the subject has been avoiding the object of his fear for years, and there are details about his answer before it that he cannot recall, or that he exaggerates while remembering it. The direct observation of these reactions from the clinician helps in the better assessment of the patient's state.

There exist two BAT types: progressive and selective BAT. In the progressive BAT, the subject is gradually exposed to the stimuli while the clinician studies his response step-by-step. For the selective BAT, the clinician chooses challenges for the subject to fulfill, in order to provoke the phobic response. During the test, subjects are asked to provide at regular periods ratings of their state, using scales such as the Subjective Units of Distress Scale (SUDS; Wolpe and Lazarus, 1966). The SUDS is composed by questions to rate between 0 (no fear) and 100 (worst fear you can imagine). These measures are joined with the evaluations taken by the clinician in contextual variables (conditions of the room), physical sensations (sweating, shaking, heart rate…), reactions of the patient (escape, avoidance…), proximity to the feared object…

However, the ecological validity of the BAT is not complete, because there are some factors that make it differ from the real reaction of the subject in his normal life. The clinical environment, for example, normally makes the subject force himself and try to approach the phobic stimuli closer than he would do in real life. For avoiding this, clinicians should work with the subject and try to personalize the task so the answers are closer to the real reactions.

Despite BAT is the most common test for behavioral assessment, some clinicians prefer the self-monitoring diaries. Those are

notebooks the patients use where they record any encounter they recall or observation about their fear they make. About each experience, they have to point out the intensity of the fear, the physical sensations, thoughts they have meanwhile… However, this kind of evaluation has been considered more as a following tool during the treatment than as a real objective measure during the assessment (Hood and Anthony, 2012).

Finally, the self-reported scales are instruments and measures designed to assess the severity of the particular phobia (Grös and Antony, 2006). Among the scales available, it can be mentioned the Fear Survey Schedule (FSS-II; Bernstein and Allen, 1969) which lists 51 items about which the subject must rate his phobia between 0 (none) and 6 (terror). The list of items includes DSM-IV related specific phobias (heights, dogs…) and questions associated to the diagnostic criteria (fear of angry people, to criticism, to crowds…).

Another scale available is the Phobic Stimuli Response Scale (PSRS; Cutshall and Watson, 2004). This one consists in a 46-item self-report questionnaire for the assessment of one of five fears: social, animal, physical confinement, bodily harm and blood-injection. However, the scales do not correspond with the criteria from the DSM-IV and sometimes are not considered appropriate (Hood and Anthony, 2012).

Finally, several specific tests exist to assess the spider phobia that concerns this Thesis. For example, the Fear of Spiders Questionnaire (FSQ; Szymanski and O'Donohue, 1995) is a reliable measure, more sensitive for the assessment in the nonphobic range. The Spider Phobia Questionnaire (SBQ; Arntz et al., 1993) is a reliable test to assess fearful beliefs and reactions of the subject. The Spider Questionnaire (SPQ; Klorman et al., 1974) assesses the verbal-cognitive component of the fear, and its value has been probed. Lastly, the Watts and Sharrock Spider Phobia Questionnaire (WS-SPQ; Watts and Sharrock, 1984) evaluates the state of vigilance, preoccupation and avoidance of spiders in the subject.

4.1.1 Use of neuroimaging techniques for the assessment of phobias

As aforementioned, many studies have taken advantage of the goodness that neuroimaging brings to analyze the brain areas related to the phobia. Those studies, however, mostly used images of real animals (pictures or videos) as stimuli during the scans. For example, Paquette et al. (2003) used film excerpts of real spiders as stimulus and excerpts of real butterflies as control. They tested 12 spider phobic subjects before and after being treated with an effective cognitive-behavioral therapy (CBT) using an emotional activation paradigm. As control, they used normal subjects with no phobia. The brain areas related to the phobia were analyzed comparing the results of the phobic subjects and the control ones before the CBT; and then, those results were compared with those obtained after the treatment, concluding that the areas that were considered related to the phobia had stopped their activation after the CBT.

The most used stimulus in previous studies has been pictures. One example is the research conducted by Schienle et al. (2007), to study the effect of a one-session cognitive therapy. In this case, they used pictures of spiders, comparing them with images that provoked fear, disgust and neutral ones. They studied phobic subjects in comparison with non-phobics. The phobics were divided in two groups: a therapy group and a waiting list group. Then comparisons were made between the patients groups, and between the patients and the controls.

Larson et al. (2006) also used pictures as stimulus in an fMRI study over phobic and non-phobic subjects to evaluate the activation of the amygdala. The special characteristic of the activation of the amygdala with phobic exposition is that it is produced early in the stimulation and then disappears. They found differences in brain activation between phobic and non phobic subjects, and between phobogenic and nonphobogenic stimuli over the phobic subjects. The differences in the amygdalar activation were found to be brief but strong over

the phobic subjects. In another study, Alpers et al. (2009) studied the amygdala activation and its relationship with attention over spider-phobic women, employing superimposed images of spiders and birds during the task. They concluded that the amygdala activation is related to attention.

Other studies that used pictures as stimuli did not focus on the analysis of the amygdala activation. It can be emphasized the work conducted by Straube et al. (2007) to analyze the anticipatory anxiety, which refers to the fear you feel when you are expecting to find the animal object of your phobia. In this study, they studied phobic and non-phobic subjects, who were exposed to blocks of pictures of spiders (fear condition) and mushrooms (control condition). The anticipatory anxiety was measured preceding each group with an anticipatory period where a symbol (% or #) was presented, which previously had been related to the specific group it represented (spiders or mushrooms). In another study, Wendt et al. (2008) analyzed the defensive response the subject experiments before the object of fear appears. They applied fMRI to analyze it, using a sustained exposure to phobia relevant stimuli. The stimuli consisted in blocks of pictures divided in 5 categories: spiders (phobia relevant), mushrooms (neutral for the contrast with the spiders), pleasant content, unpleasant content and complex neutral pictures.

Although it has been already decided the use of fMRI for this part of the Thesis instead of EEG or any other neuroimaging technique, it may be interesting to point out some previous works developed with those other techniques. For example, on one hand Scharmüller et al. (2011) used EEG to investigate the symptoms of spider phobia, using pictures as stimulus. Phobic and non-phobic subjects were exposed to phobia-relevant, generally fear-inducing, disgust-inducing and neutral pictures while their brain electrical signals were measured via an EEG headset. They used the sLORETA tool to locate the specific brain areas activated from the EEG results. On the other hand, Furmark et al. (2002) analyzed the effects of Citalopram and CBT

therapy over phobic subjects using PET images, but in this case for the study of the social phobia. They assessed the regional cerebral blood flow (rCBF) in 18 untreated patients during an anxiogenic public speaking task. The subjects were divided in three groups: the first was treated with citalopram medication, the second with CBT and the third was not treated at all. Then they repeated the scanner after 9 weeks of treatment or waiting-list. They found similar significant improvements in the citalopram and CBT groups, while the waiting-list group remained unchanged.

4.1.2 Treatment of specific phobia

For the treatment of phobias, different methods have been used over the years, from schedules consisting in intensive exposure sessions of three or four hours to step-by-step approaches which last several weeks. More recently, the introduction of Virtual Reality in the treatment of phobias has widen the possibilities of this treatments, allowing not only the interaction between the patient and the feared object in a more controlled space, but also the personalization of the virtual world according to the subject's phobia. In this section, a review of the traditional treatments used until now as well as of the new branches of the treatment using VR will be made.

4.1.2.1 Traditional treatment of specific phobias

The most commonly applied method for the treatment of phobias has been until now the in vivo exposure, although other exposure-based methods and cognitive approaches are also used. As aforementioned, the duration of these treatments is changeable, and could vary from few hours to several weeks. However, what is demonstrated is that after two or three hours of treatment, the first advances can be observed (Choy et al., 2007). Following, the most commonly used methods for the treatment of specific phobias will be exposed.

Exposure-based treatment

It has been proved to be the best way of approaching a specific phobia, with results observable from the first session (Choy et al., 2007). The exposure therapy consists in the gradual exposure to the feared object or situation, always in a controlled environment and with a progression dependent on the patient's response, while preventing behavioral and cognitive avoidance. Depending on the nature of the fear, it can involve exposure to the feared object or situation, interoceptive cues (such as internal physical sensations), or a combination of both (Hood and Anthony, 2012).

Although the final aim is always the same (the total approach to the feared object or situation), the pacing of the exposure and the timing between sessions varies between treatments. Some therapists perform one-session treatments in which the subject is overexposed to their fear and in a few hours they are able to deal with it (for example, to interact with their feared animal). Others prefer a more spaced method where two or three one-hour sessions are performed every week, and where the exposure is increased progressively according to the subject's reactions. Those methods normally begin with a low-arousal stimulus like pictures or videos, and increase the intensity until the arrival to the in vivo exposure. However, the final aim is always the same: to make the patient remain in the situation enough time to learn about the real consequences of the stimuli (contrary to their believed feared responses; for example, a spider does not persecute you and more likely, it will try to run from you) and to reduce the fear and anxiety felt to a tolerable level.

The in vivo exposure has demonstrated to produce the greater improvements between the specific phobia's treatments, normally outperforming the other active treatments; including imaginal exposure, relaxation and cognitive therapy (Wolitzky-Taylor et al., 2008).

There are several variables to take into account while designing the in vivo method to use with a particular patient. As aforementioned, the duration of the exposure and the pacing between sessions is

important; however, there are more issues to keep in mind. The intensity of the exposure is one of them. It is thought that moderate intensity fear is needed to provoke the extinction of the fear by learning its real consequences; however, if it is better the gradual approach to the fear or the flooding into the fearful situation depends on the subject's reaction. What is known is that the progressive exposure is more tolerable, and may be recommended in cases of patients reluctant to complete the therapy or with high levels of phobia (Craske et al., 2008). It has been also recommended to adapt the duration of the exposure to the subject's progression, instead of stating a fixed time. This would allow the patient to take the time he needs to disconfirm any false beliefs he had about the feared object or situation. Finally, another important variable to take into account is the contextualization of the stimuli. Although the subject may have successfully completed the extinction learning inside one context, this may not be extended to other settings or stimuli. Therefore, it is important to extend the exposure therapy to different environments and stimuli (for example, spiders with different sizes, shapes and activity levels), in order to generalize the gains of the therapy to real world encounters (Rowe and Craske, 1998).

Cognitive Therapy

The cognitive therapy consists in challenging the subject's beliefs, expectations or predictions about the likelihood or consequences of harm related to the encounter with the feared object or situation, in order to reduce the anxiety and avoidance behavior (Hood and Anthony, 2012). Cognition plays an important role in the maintenance of the phobia, so a treatment centered in its modification may be a powerful tool in the extinction of the fear. However, although proved to be more effective than not doing anything, the cognitive therapy is less effective than the in vivo exposure for the treatment of specific phobias, and its use should be

considered as a complement to the former more than as a substitute to it.

Pharmacotherapy

The third kind of treatment used in specific phobias is the pharmacotherapy or use of anxiolytic medications for the reduction of the phobia's symptoms to improve the results of the treatment. However, the efficacy of this technique has not been proved; and several studies evidence that their use may not be beneficial to the treatment and that the patients may relate the gains obtained by the therapy to the medication, relapsing in the phobia once the pharmacotherapy is finished. This leads to an increase in the relapse in the follow-ups (Choy et al., 2007).

However, there appears to be an exception in the use of d-cycloserine (DCS), a partial agonist of the N-methyl-D-aspartate (NMDA) glutamatergic receptor, which has been proved to accelerate the fear reduction during the in vivo exposure (Norberg et al., 2008). The benefits of DCS do not rely on its anxiolytic properties, but in the reinforcement of the memory consolidation after the treatment period (Hood and Anthony, 2012).

4.1.2.2 Virtual Reality in the treatment of phobias

In the field of phobias, Virtual Reality (VR) has been repeatedly used to treat the disorder, up to now has not been used for the assessment of the disturbance yet. One of the more common treatments for mental disorders are the cognitive-behavioural treatments (CBT), based on the exposure of the subject to the object of their fear, to make them adapt progressively to the stimulus (Frueh et al., 1995; Olatunji et al., 2009). However, these direct-exposing techniques sometimes are considered "dangerous and ethically reprehensible" (Olatunji et al., 2009; Feeney et al., 2003; Prochaska and Norcross, 1999), because of the impact that the direct exposure can have over the subject. In this sense, VR allows to expose the subject to the feared stimuli in a controlled environment

that is considered safer and more ethically acceptable (Richard and Gloster, 2007). Botella et al. (2006) gave a list of the advantages that VR has in psychotherapy; of which it can be first emphasized the aforementioned allowance of running the therapy in a protected environment close to reality, where the patient can act without feeling threatened (from a "safe base"). Furthermore, in VR the patient can interact with the context and the psychotherapist can grade the situation according to the patients' state. Moreover, in a more technical way, VR is an excellent source of information in performance achievements and allows an accurate control of the situation. At last, it can be mentioned the ecological validity of the stimuli presentation.

One of the main advantages of VR is that it allows the patient to interact with the phobic object or situation, as if they were real and he were there with the feared animals. If the VR is successful, it will activate the feeling of presence in the subject, as aforementioned in the previous section; and that is why it was performed the presence study before this one. As Schuemie and van der Mast (2001) stated, if the user can perceive the virtual world as the real one, it will evoke similar responses from the user as the real world, making it possible to treat the phobias in VR with the same effectiveness as in the real world. However, this is not easy to achieve, because systems for treating phobias have unique requirements. One interesting study in this field is the one conducted by Juan and Calatrava (2011), who tested an augmented reality (AR) system for the treatment of small animals' phobia using an optical see-through (OST) head mounted display (HMD), and comparing it with a similar video see-through (VST) HMD. They tested non-phobic population and measured their sense of presence and anxiety with both systems. They found that when considered all the participants together, the VST induced a greater sense of presence, while when analyzing only the subjects with more fear, the two systems induced the same sense of presence. In terms of anxiety, both systems provoke similar levels.

The VR exposure therapy (VRET) has been widely used in the treatment of specific phobias (Krijn et al., 2004), such as acrophobia (Rothbaum et al., 1995a), claustrophobia (Botella et al., 1998), spider phobia (Carlin et al., 1997), fear of driving (Wald and Taylor, 2000), and fear of flying (North et al., 1997a). In VRET, the subject is gradually exposed to a negative stimulus, in order to reduce the anxiety provoked, which makes the experience less intimidating and less expensive than traditional treatments (Bush, 2008). One example of this kind of treatment in the field of small animals phobia is that developed by Garcia-Palacios et al. (2002), using VR over spider phobic subjects. They compared the answers given to phobia questionnaires by two groups: one that was treated with a VR exposure therapy (four one-hour sessions) and another which was not treated at all. They found a clear improvement in the VR group, showing the 83% of the patients a significant improvement. Botella et al. (2010) have also applied augmented reality for treating cockroaches' phobic subjects. They tried to demonstrate that AR could be an effective alternative to the in vivo exposure, which is sometimes considered too aggressive and ineffective. They applied one-session AR exposure therapy over 6 subjects, testing the results in the short and long term. They found that all participants improved significantly in all the outcome measures after the treatment, results which were maintained in the long term tests. However, until now VR has not yet been used inside the fMRI as a stimulus to assess the responses of phobic subjects in the presence of the feared elements.

Here the proposal is that the use of VR as stimulus in fMRI environments will entail the same advantages to the phobia evaluation that it brought to the phobia treatment. It will make possible to place patients in virtual situations related to the object of their phobia, where they will be able to interact. VR can make the user feel present in the environment, helping the patient to experience it in a more similar way to the real situation than when you see videos or photographs (Krijn et al., 2004). Consequently, it is expected that the activated brain areas will be more similar to those

activated in the real experience. This is the main improvement of the use of VR with respect to other kinds of stimuli such as images or videos. Furthermore, the experimenter will have the possibility of controlling the exposure to the virtual situations in the most convenient way, grading it in different levels, if it is required. Finally, behavioral evaluations about the responses of the participants inside the virtual environment may be easily monitored with this kind of systems.

In order to validate this proposal, the target in the present course of work is to examine if VR can be used for the assessment of the phobia, provoking a more realistic and immersive situation than the view of a still photograph, that can be manipulated by the psychologist. Virtual environments where the subject can navigate freely, which should induce a higher sense of presence due to the self-control of the navigation route (Alcañiz et al., 2009), have been used. The main hypothesis is that the brain areas activated with these environments will be coherent with results from previous studies based on pictures or videos of real animals. The validation of this proposal would fulfilled at the same time the hypothesis of this PhD Thesis, demonstrating whether or not VR combined with neuroimaging can help in the assessment of the patient's state during the undergoing of a psychological treatment, providing valuable information that could help in the adjustment of the therapy itself to the patient's brain activation patterns, in accordance with the new neuropsychotherapy theory.

4.2 Materials and Methods

4.2.1 Subjects

For this study, there were recruited 11 right-handed phobic women, aged between 20 and 35 (mean age 24.64). They passed through two fMRI scans, one before the treatment and another one month after completing it. None of them had any other medical or psychological disorders, apart from the phobia. The participants' hand dominance

was tested using the Edinburgh Handedness Inventory (Oldfield et al., 1971) (see Appendix 3).

The diagnosis and assessment phase was conducted by expert clinicians who were also the therapists for the participants. In order to be included in the study, the following inclusion criteria were considered: meeting DSM-IV (American Psychiatric Association, 2000) criteria for Specific Phobia animal type (see Appendix 5), specifically Cockroach and Spider Phobia, having scores over 4 in phobic avoidance (on a scale of 0 to 8), having no current alcohol or drug dependency, having no diagnosis of major depression or psychosis, not having been or being treated with a similar program and having a minimum of 1 year of duration for the problem. The Anxiety Disorders Interview Schedule (ADIS-IV; DiNardo et al., 1994) specific phobia section was used to conduct the differential diagnosis of the anxiety disorders included in the DSM (see Appendix 6).

These women were students, were paid for their participation in the study and were recruited from the Universitat Jaume I in Castellón. Each subject signed a written informed consent prior to participation.

4.2.2 Environments

The virtual environments used during the task were programmed using GameStudio software (Conitec Datensysteme GmbH, Germany), which allowed the development of 3D objects and virtual worlds with which participants could interact and navigate. The environments were the same for both scans (pre- and post-treatment). For this study the task was divided into three experimental conditions, all of them involving a room where the subject could navigate freely:

- In the first of these conditions ('CLEAN'), the patient navigates through a common clean bedroom (with a bed, a closet, and a desk with some books on it).

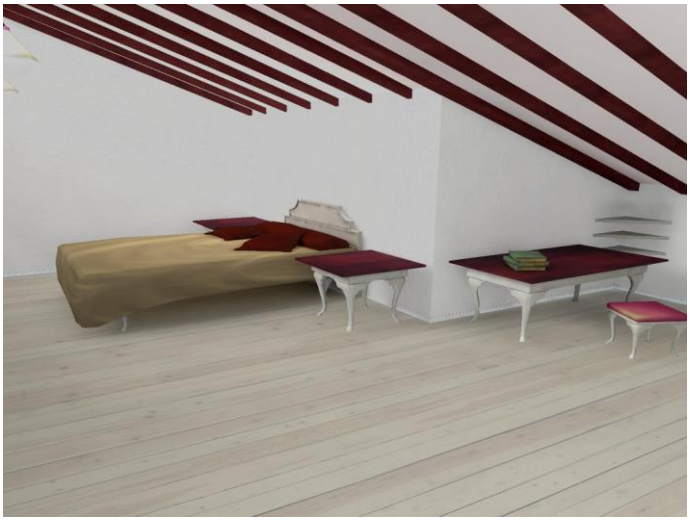


Figure 4.1 Capture of the “CLEAN” environment

- In the second condition (‘DIRTY’), the navigation is performed through the same room, but this time dirty and darker, giving the subject the feeling that the feared animal could appear in any moment; this room pretends to stimulate the anxiety in the user.

Figure 4.2 Capture of the “DIRTY” environment

- In the last condition ('PHOBIC'), the subject navigates through the same dirty room, but this time there appeared spiders and cockroaches.

Figure 4.3 Capture of the "PHOBIC" environment

Each of these experimental conditions lasted 20 seconds.

To prevent the subjects from staying still during the navigation periods, a search task was included in order to force them to move through the environment and confront the phobic stimulus in the correspondent experimental condition. This task consisted on searching and counting the number of red keys that appeared and disappeared in the environment. However, they were not encouraged to find them all, or to find them as quickly as possible, they were only told to continue searching for them during each period. After each task, subjects were questioned about the number of keys they had found (they had to answer in a short period of 4 seconds). While they were conducting the tasks, the researcher checked in the computer that they had answered properly. The number of keys that they counted was not relevant, it was just included to avoid that the subjects remained still during the experimental conditions.

(a) (b)

Figure 4.4 (a) Capture of one red key inside the environment, (b) capture of one of the signs asking for the number of keys seen

A black screen was included between phases to give subjects a rest period during which brain activation could decay to its baseline values (6 seconds). After this, the label indicating the next task appeared (2 seconds). The total time between tasks was 12 seconds. Each of the three experimental conditions was repeated six times in a counterbalanced order to prevent effects produced by the order in which they were presented. At the beginning of the experiment there were 14 seconds of black screen to compensate for T1 saturation effects. The total time of the complete experiment was 9 minutes 40 seconds. A scheme of the protocol can be seen in Figure 4.5.

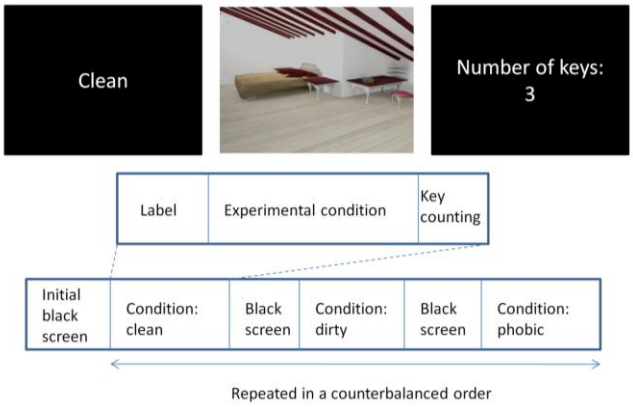


Figure 4.5 Scheme of the protocol

Before entering the scanner, subjects underwent a short training session where they were introduced to the VR navigation task. This training session was conducted in a supplementary virtual environment, without any kind of phobic stimuli, to avoid habituation (the VE used were the same used in the presence study, and a capture of them can be seen in Figure 3.5). During the fMRI scan, the VR application checked the total time that they spent moving the joystick in each condition to guarantee that they did not remain still during the phobic stimulation.

4.2.3 fMRI procedures

The fMRI procedures used for all the subjects were the same for both scans (the pre-treatment and the post-treatment). All subjects were scanned in a 1.5 Tesla Siemens Avanto Magnetic Resonance scanning device (Erlangen, Germany). An adapted magnetic resonance (MR) helmet was used to prevent head movement. To display the environments, MRI-compatible video goggles, VisualStim Digital (Resonance Technology Inc., Los Angeles, USA) were used; and, for the navigation, an adapted joystick (Resonance Technology Inc., Los Angeles, USA). First, sagittal T1-weighted structural images were acquired (224 x 256 matrix covering the brain with 176 contiguous 1 mm slices, TR = 11 ms, TE = 4.94 ms, FA = 15^{o}, voxel size = 1.04 x 1.04 mm). Then, the functional scanning was launched, synchronized with the virtual environments. Functional images were obtained using a T2* single-shot echo-planar imaging (EPI) sequence. There were 30 contiguous 4.2 mm interleaved axial slices (parallel to the AC-PC line) covering the entire volume of the brain with a 64 x 64 matrix (TR = 2000 ms, TE = 30 ms, flip angle = 90^{o}, voxel size = 3.5 x 3.5 mm).

4.2.4 Data Analysis

Similarly to what was done in the presence study, the Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) was used for the analysis of the fMRI data, launched with the 7.1 version of Matlab (MathWorks, Natick, Massachusetts, USA). The first 7 scans were excluded from

the analysis to eliminate the decay of the fMRI signal that is associated with the moment when magnetization reaches equilibrium. The first step taken was to align the images to the AC-PC line. Once it was done, the preprocessing of the data began, realigning the functional images (estimate and reslice option), coregistering them to the structural images and segmenting this latter anatomical scan. Then it was performed the normalization of the resliced functional volumes with the normalization parameters extracted after segmentation and normalization of the anatomical volumes for each subject separately (the template was provided by the Montreal Neurological Institute). None of the volunteers had to be excluded due to movements or distortions during the fMRI. Finally, the images were smoothed using a Gaussian kernel (FWHM of 8 x 8 x 8 mm).

In a first fixed-effect level analysis, the functional time series for each subject and for each condition were modeled with a box-car function convolved with the hemodynamic response function. The parameters for the motion correction were employed as regressors of non-interest. To eliminate the low frequency components in the signal, caused by the scanner motion and warming, a 96 s high pass filter was applied.

Until now the analysis has been the same for all the subjects and scans. Now it will be distinguished between the analysis for the pre-treatment scans and the analysis for the comparison pre-post treatment.

For the pre-treatment scans, once done the preprocessing and the first level analysis, group tests at a second level random effect analysis were performed. The data was looked for task related activation by performing a one-sample t-test including contrast images of estimated parameters for the differences of interest between conditions. As aforementioned, the fMRI paradigm was divided into three different navigation tasks (clean room, dirty room and phobic-stimulus room) that will be compared in order to obtain

the contrasting brain activations. Although the results for the three contrasts have been obtained, the results that show the brain activations for the phobic stimulus are contained in the "phobic>clean" contrast. The "phobic>dirty" contrast shows phobic activations avoiding the anxiety feeling caused by the dirtiness of the room, and the "dirty>clean" contrast contains the anxiety related activations.

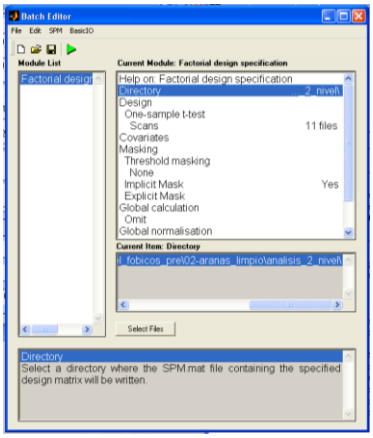


Figure 4.6 Capture of the batch editor for the second level analysis

All contrasts at group level were considered if more than 10 adjacent voxels passed the statistical threshold of $p < 0.005$ (uncorrected). These results were corrected at $p<0.05$ using AlphaSim correction (combined height threshold $p<0.005$ and a minimum cluster size= 25) (Song et al., 2011).

AlphaSim is a tool that allows you to calculate, depending on the mask used during the fMRI images analysis, the minimum number of voxels that a cluster should have to consider it corrected by the Monte Carlo correction. For doing so, the Rest application from Matlab was launched, and when the window appeared, selected the Utilities button.

Figure 4.7 Captures of the REST tool

The REST AlphaSim button opens the AlphaSim application. In it, it is indicated: the FWHM (smooth used in SPM, 8mm), rmm or number of neighbors to consider (typically 1.5xvoxel size), p threshold (voxel statistical threshold used in SPM, 0.005), number of iterations to make, mask (the file "mask" generated by SPM when the analysis was performed), output dir (where the output file will be saved) and output name for this file. When clicked the Run button, the process begins.

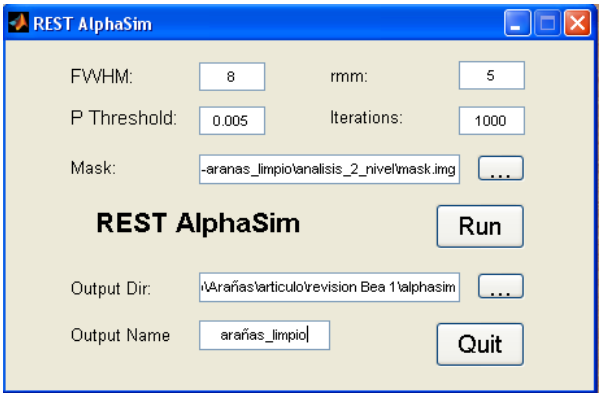


Figure 4.8 Capture of the REST AlphaSim window

The output file was opened using WordPad and searched for the information looked for.

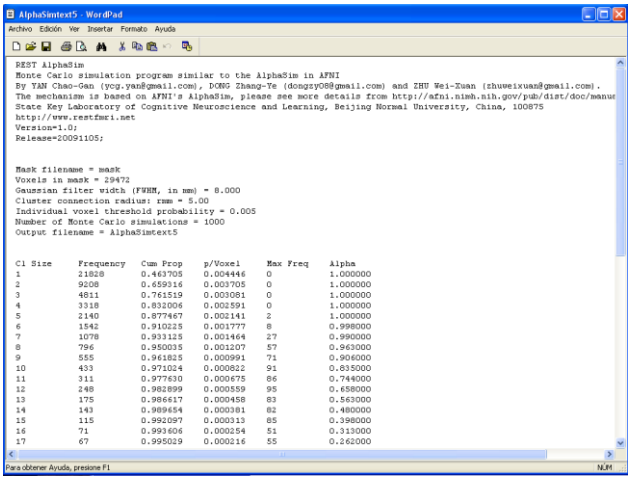


Figure 4.9 Capture of the AlphaSim results, opened with WordPad

In the last column of the file can be seen the value of the corrected alpha. For a value of p<0.05 corrected, it is looked for in the last column, and check the cluster size needed to meet it in the first column. In this case, any cluster with 25 or more voxels will be considered corrected at p<0.05.

19	38	0.997005	0.000144	28	0.162000
20	30	0.997642	0.000119	27	0.134000
21	26	0.998194	0.000099	25	0.107000
22	16	0.998534	0.000080	16	0.082000
23	8	0.998704	0.000068	8	0.066000
24	11	0.998938	0.000062	10	0.058000
25	8	0.999108	0.000053	7	0.048000
26	11	0.999341	0.000046	10	0.041000
27	5	0.999448	0.000037	5	0.031000
28	6	0.999575	0.000032	6	0.026000
29	1	0.999596	0.000026	1	0.020000
30	2	0.999639	0.000025	2	0.019000
31	2	0.999681	0.000023	2	0.017000
32	0	0.999681	0.000021	0	0.015000
33	1	0.999703	0.000021	1	0.015000

Figure 4.10 Capture of the AlphaSim results, with the one chosen remarked in blue. For a p<0.05 it is needed a cluster of 25 voxels or more

For the pre-post treatment comparison, again after the preprocessing and the first level analysis for the post-treatment scans (the pre-

treatment scans were already processed in this step from the previous part) group tests at a second level random effect analysis were performed, testing for task related activation by performing a two-sample t-test including contrast images of estimated parameters for both groups of images (the parameters obtained from the pre-treatment images and those obtained in the post-treatment images) for the differences of interest between conditions. More exactly, the results for the "phobic>clean" contrast, that show the results of brain activations for the phobic stimulus in comparison with the control condition, were obtained for the comparisons "pre-treatment>post-treatment" and "post-treatment>pre-treatment".

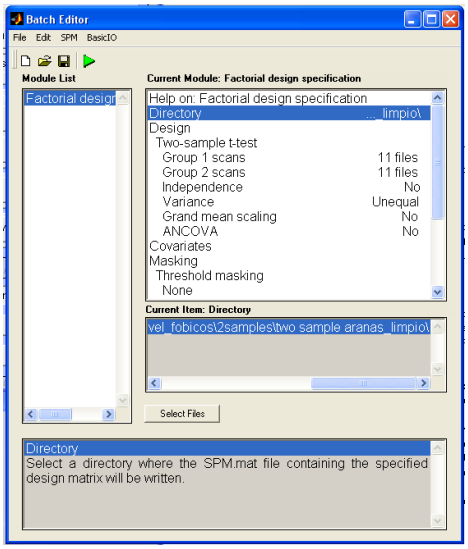


Figure 4.11 Capture of the batch editor for the second level analysis in the pre-post study

In this case, all contrasts at group level were considered if more than 10 adjacent voxels passed the statistical threshold of $p < 0.005$ (uncorrected). It was used the xjView (http://www.alivelearn.net/xjview8/) software utility for SPM (that uses the MNI coordinates system) to obtain the specific brain areas that were activated in each contrast.

4.3 Results

4.3.1 Results for the pre-treatment fMRI scan

First, the contrast "phobic > clean" was selected and looked for the main activated brain regions. Activations were found in the left occipital inferior lobe and middle occipital gyrus bilaterally among others (see Table 4.1 and Figure 4.12). Other brain regions which displayed significant activations during the task were the cuneus bilaterally, the superior frontal gyrus and the precuneus.

Anatomical region	Hemisphere	x (mm)	y (mm)	z (mm)	t score	Cluster size	p
Occipital Inferior Lobe	L	-22	-98	-12	4.19	36	p<0.05 corrected
Middle Occipital Gyrus (BA19)	L	-54	-77	-4	5.21	29	p<0.05 corrected
Middle Occipital Gyrus	R	31	-77	0	4.76	175	p<0.05 corrected
Cuneus	R	20	-91	9	4.01	36	p<0.05 corrected
BA18	R	26	-96	6	-11.64	28	p<0.05 corrected
Cuneus	L	-8	-95	30	5.82	55	p<0.05 corrected
Superior Frontal Gyrus	R	20	49	42	4.52	13	p<0.005 uncorrected
Precuneus	L	-1	-46	68	4.59	31	p<0.05 corrected

Table 4.1 Brain area activation results for the "phobic > clean" contrast

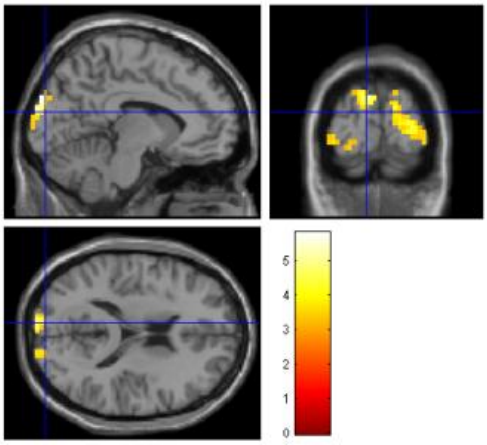


Figure 4.12 Brain activations for the "phobic>clean" contrast

In Table 4.2, the results obtained for the "phobic > dirty" contrast, which include activations in the inferior occipital lobe and superior and middle frontal lobe, can be observed. Those results can also be seen in Figure 4.13.

Anatomical region	Hemisphere	x (mm)	y (mm)	z (mm)	t score	Cluster size	p
Inferior Occipital Lobe	L	-26	-98	-12	5.52	54	p<0.05 corrected
Inferior Occipital Lobe	R	48	-84	-8	4.43	22	p<0.005 uncorrected
Superior Frontal Lobe	L	-22	56	34	4.51	18	p<0.005 uncorrected
Middle Frontal Lobe	L	-26	14	63	5.25	18	p<0.005 uncorrected

Table 4.2 Brain area activation results for the "phobic > dirty" contrast

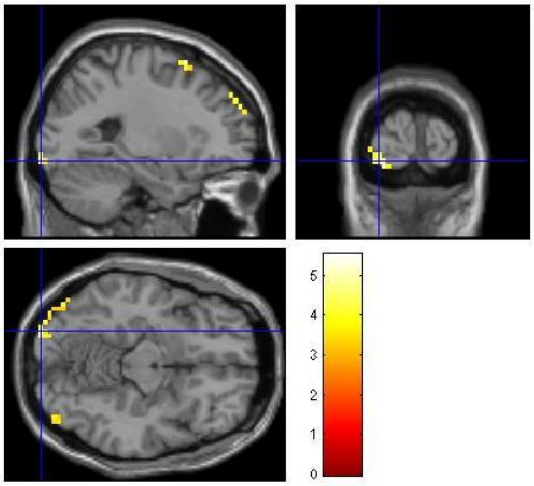


Figure 4.13 Brain activations for the "phobic>dirty" contrast

Finally, in Table 4.3, there can be observed the results obtained for the "dirty > clean" contrast, with activations in the occipital and frontal lobes and the cingulated gyrus. Those results can also be seen in Figure 4.14.

Anatomical region	Hemisphere	x (mm)	y (mm)	z (mm)	t score	Cluster size	p
Superior Occipital Lobe	L	-15	-91	30	5.69	201	p<0.05 corrected
Middle Frontal Gyrus	R	24	53	-8	5.23	39	p<0.05 corrected
Middle Occipital Gyrus	R	27	-84	13	6.81	184	p<0.05 corrected
Cingulate Gyrus	R	17	-35	30	7.40	14	p<0.005 uncorrected

Table 4.3 Brain area activation results for the "dirty > clean" contrast

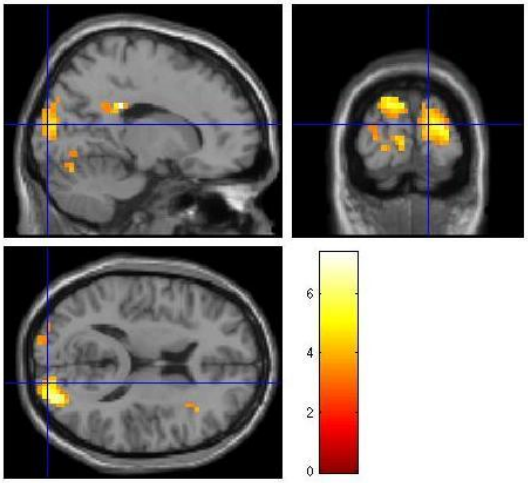


Figure 4.14 Brain activations for the "dirty>clean" contrast.

4.3.2 Results for the pre-post comparison

For the "pre-treatment>post-treatment" contrast, activations were found in the right superior frontal gyrus and the left supplementary motor area (see Table 4.4 and Figure 4.15).

Anatomical region	Hemisphere	X(mm)	Y(mm)	Z(mm)	T score	Cluster size
Superior Frontal gyrus	R	20	46	47	4.11	10
Supplementary motor area	L	-5	25	63	3.69	6

Table 4.4 Brain activations for the "phobic>clean" contrast, for the comparison "pre-treatment>post-treatment"

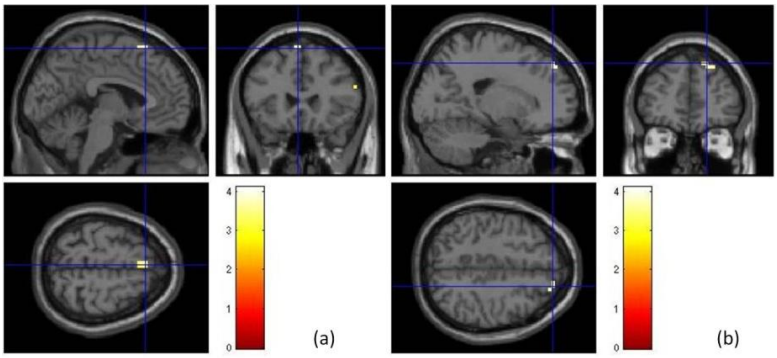


Figure 4.15 Brain activations for the "phobic > clean" contrast, for the comparison "pre-treatment>post-treatment". The image on the left (a) shows the brain activation centered on the supplementary motor area, and the image on the right (b) centered on the superior frontal gyrus.

For the "post-treatment>pre-treatment" contrast, activations were found in the right cerebellum, left sub-gyral temporal lobe, left thalamus, right inferior frontal gyrus, left inferior parietal lobe, left sub-gyral frontal lobe and right middle cingulum (see Table 4.5 and Figure 4.16).

Anatomical region	Hemisphere	X(mm)	Y(mm)	Z(mm)	T score	Cluster size
Cerebellum	R	13	-49	-16	4.57	16
Sub-gyral temporal lobe	L	-43	-49	0	3.21	6
Thalamus	L	-22	-28	13	4.03	15
Inferior frontal gyrus	R	48	0	21	4.84	13
Inferior parietal lobe (BA 40)	L	-40	-46	38	3.75	25
Sub-gyral frontal lobe	L	-22	4	42	3.27	13
Middle Cingulum	R	17	-21	47	3.69	8

Table 4.5 Brain activations for the "phobic>clean" contrast, for the comparison "post-treatment>pre-treatment"

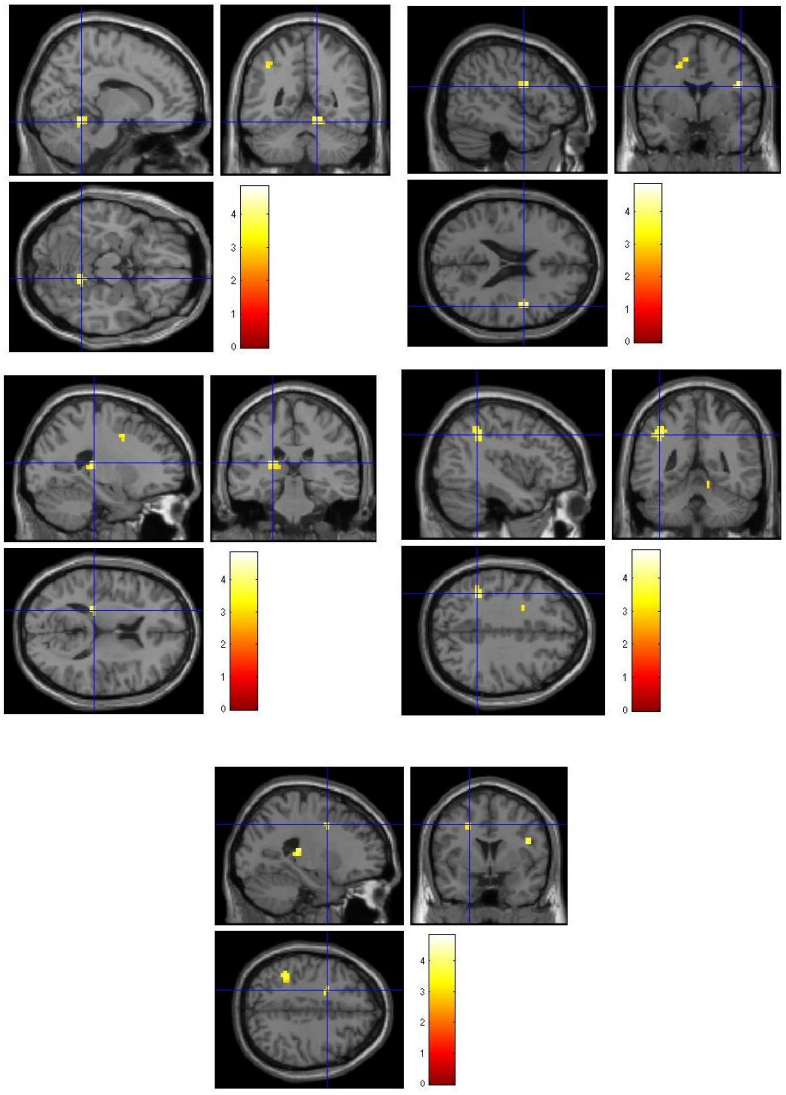


Figure 4.16 Brain activations for the "phobic > clean" contrast, for the comparison "post-treatment>pre-treatment". The captures are centered in the: a) right cerebellum, b) right inferior frontal gyrus, c) left thalamus, d) left inferior parietal lobe and e) left sub-gyral frontal lobe.

4.4 Discussion

In this section, the discussion of the results for both the phobia studies will be presented. Later, in the next section (4.5) those

arguments given to the phobia studies will be translated in terms of the objectives fulfilled from the Thesis goals.

4.4.1 Discussion of the results for the pre-treatment fMRI scan

The main goal of the present phobia study was to analyze the brain areas activated due to phobic stimulus during navigation through a virtual environment in the three different experimental conditions previously described (CLEAN, DIRTY and PHOBIC). One of the main results for the purposes of the study are those obtained when comparing brain activations between phobic and clean conditions ("phobic>clean"), which are those that reflect the fear and anxiety felt by the subjects due to the phobic stimulus when compared with a emotionally neutral situation. Both the phobic and dirty situations may generate anxiety in the participant. However, in the dirty condition the anxiety is generated by the fact of being in a threatening room (because of the dirtiness of the room, the participant may feel that is a dangerous place to be in) and in the phobic condition, apart from the dirtiness of the room, there are phobic stimuli, spiders and cockroaches that will generate a phobic specific activation in the brain. In the "phobic>clean" comparison the activations may be caused by both factors. The activations obtained in the "phobic>dirty" contrast would be directly related to the phobia itself, and not to the anxiety feeling.

In the following paragraphs, the results of the "phobic>clean" contrast will be commented in comparison with results obtained in other studies about phobia. After that, the results obtained in the other two contrasts will be briefly discussed. Finally, some overall conclusions will be made.

One of the most important activated areas in the "phobic>clean" contrast is the occipital lobe, more specifically, activated in its left inferior area and in the middle lobe bilaterally. Other important result is that obtained in the superior frontal gyrus. At last, activations were found in the cuneus and precuneus.

The occipital lobe mainly controls the visual areas, which are necessary for the performance of a navigation task. In the inferior area of the occipital lobe, it has been found activation in the lingual gyrus, believed to play a role in dreaming as well as in vision, especially in the recognition of words (Poza and Martí, 2006). In this area, it was also found activation in the Brodmann area 18, part of the extrastriate visual cortex. This encompasses multiple functional areas, including V3, V4, V5/MT, which is sensitive to motion or the extrastriate body area (EBA) used in the perception of human bodies (Orban, 2008; Astafiev et al., 2004).

In a similar study conducted by Paquette et al. (2003), using film excerpts of spiders as the phobic stimulus and film excerpts of butterflies as neutral condition, they found a similar activation in this area when subtracting spiders' minus butterflies' contrasts. They concluded that this activation was related with enhanced visual attention to the phobic stimuli, and support vigilance functions in anxiety (Fredrikson et al., 1993, 1995). Moreover, those results are consistent with others obtained in other similar studies (O'Craven et al., 1997; Büchel et al., 1998; Chawla et al., 1999). More recently, there have been several fMRI (Schienle et al., 2007; Alpers et al., 2009; Straube et al., 2007) and PET (Scharmüller et al., 2011) studies among phobic and non-phobic subjects that have also found activation in the visual cortex. In fact, Straube et al. (2007) justified it as likely to be caused by the attention subjects put on the visual input that reflect an "increase in the processing of the cue but also the expectation of behaviorally relevant sensory input". Moreover, several studies have pointed out the spread of the amygdala activation to the occipital areas due to the emotional relevance of the stimulus (Aggleton, 1993; Krolak-Salmon et al., 2004).

The other important activation is found in the superior frontal gyrus. This area is related to the feeling of self-awareness (Goldberg et al., 2006), which is increased when the phobic subject watches the animal that provokes his fear. During a resting situation, the subject

relaxes and is less conscious of himself. But, when the phobic person finds himself in a fearful situation, his alert state increases, trying to inhibit his reaction in front of the phobic stimulus (Paquete et al., 2003). The natural reply to this stimulus is to avoid the fear response it provokes over him, and to do so he controls his mind and body, increasing the consciousness he has of himself. That is why it is considered the activation of the superior frontal gyrus essential in the reaction of a phobic situation. According to du Boisgueheneuc et al. (2006), the superior frontal gyrus is related to higher cognitive functions and working memory. Although Paquette et al. (2003) did not find activation in it, they discussed the relation of the frontal activations with the voluntary self-regulation of emotion. More exactly, they exposed the results obtained in a PET study conducted by Johanson et al. (1998), who observed an increase in the frontal rCBF (regional Cerebral Blood Flow) correlated with the use of cognitive strategies to cope with the phobic situation. Paquette et al. (2003) pointed out that the phobic subjects activated their prefrontal areas when attempting to control their fear before the film excerpts of spiders. Another explanation is given by Goldberg et al. (2006), who analyzed the subjective awareness feeling and its relation with the frontal areas of the brain. They remarked how when watching an absorbing movie or being involved in a highly demanding sensory task (as is in this case the virtual navigation through an immersive environment) the strong subjective feeling is of “losing the self”, or, as they explained, of disengaging from self-related reflective processes. Accepting this state, the increase in the self-awareness feeling during a highly demanding navigation task in the visualization of phobic stimulus is clearly related to the higher feeling of yourself when “fighting” the fear. In words of Scharmüller et al. (2011), increased activation in the superior frontal cortex might reflect patients’ urge to flee during the confrontation with the feared object; and this link between the sensorimotor system and the affective/cognitive function is in line with the theory about embodied cognition (Garbarini and Adenzato, 2004). In conclusion, it can be considered this activation essentially related to the phobia.

Activity was also found in the cuneus and the precuneus. Regarding the cuneus, it is related to visual processing, which is directly associated with the sense of presence that the subject feels while navigating through a virtual environment (Perani et al., 2001). On the other side, the precuneus is related to self-consciousness, such as reflective self-awareness, that involves rating your own personality traits (Kjaer et al., 2002; Lou et al., 2004). This information continues with the idea of an increase in the consciousness of yourself while you are exposed to a phobic stimulus, trying to reduce your reaction before it. It is also involved in directing attention in space when planning or performing a movement (Cavanna and Trimble, 2006; Kawashima et al., 1995), which is directly related with navigation through a virtual environment.

Although one of the areas most commonly related to phobias is the amygdala, it is not activated in the results of this study. However, this lack of activation is supported by several previous studies that have analyzed the pattern of activation of this area (Larson et al., 2006; Alpers et al., 2009; Paquette et al., 2003), concluding that the amygdala suffers habituation over time (Larson et al., 2006). Paquette et al. (2003) also pointed out that this suggests that the amygdala may not be related to the phobic expression or experience, but to the fear conditioning (LeDoux, 1993; Paquette et al., 2003). Straube et al. (2007) also discussed that the amygdala activation may occur during brief presentations of the phobogenic stimuli and in the induction of rapid behavioral responses more than in the sustained and explicit processing of the threatening stimuli. Alpers et al. (2009) also pointed out that their activation in the amygdala was helped by the brief stimulus they used (200ms). In the case of this Thesis, the use of periods of navigation as stimulus instead of pictures may be the cause of not detecting activation in this area (a block design was used for the protocol instead of an event-related). In fact, most of the studies around the amygdala have reported its activation during the very early stages of the stimulus (Larson et al., 2006; Schienle et al., 2007; Alpers et al., 2009).

Having exposed the main results for the “phobic>clean” contrast, there will be briefly discussed the results for the remaining contrasts. Regarding the “phobic>dirty” comparison, it was found that the inferior occipital lobe played a major role in the fear response to the phobic stimulus, bilaterally. This is in concordance with the results obtained for the “phobic>clean” contrast, where it was pointed out the relation of this area with the phobic response. As aforesaid, the occipital lobe is related to enhanced visual attention to the phobic stimuli (Fredrikson et al., 1993, 1995). The other important activation is located in the superior and middle frontal lobe, result also contained in the previous results, due to its relation with the feeling of self-awareness and the action of the sensory system (Goldberg et al., 2006). As can be seen, the main results that were highlighted as related to the phobia are still activated when the conditions of the contrast are restricted to avoid the anxiety results.

Regarding the “dirty>clean” contrast, the self-awareness is still high, due to the greater fear of finding a spider or cockroach when navigating through a dark and dirty environment than when navigating through a clean one, which results in the activation of the middle frontal gyrus. The activation of the occipital lobe is maintained here due to the higher visual processing when expecting the appearance of a feared animal. The last activation was located in the cingulate gyrus, which Paquette et al. (2003) pointed out to be mainly associated with the cognitive/internal generation of emotional state by evoking visual imagery or memories. As aforementioned, the activations in this contrast are due to the evocation of the fear, not to the exposition to it; so the meaning of the activation in the cingulate gyrus is clear as a generator of emotional evocations.

In conclusion, similar results in terms of fMRI brain activations have been obtained with VR to those obtained using real stimuli. In fact, the main activations found in the occipital and frontal areas are coherent with those found in previous studies conducted with spider

phobic subjects using pictures or videos of real animals as stimuli. Moreover, the activation in the cuneus could be related to the sense of presence elicited in the subjects because of the navigation through the virtual environment. This finding opens the door to deeper investigations over the phobias, due to the fact that VR allows recreation of normal life scenes in a more realistic and interactive way, that are impossible to achieve with other techniques. This kind of situations could allow, for example, the study over subjects with a mild phobia, whose fear can't be excited only by the use of photographs.

4.4.2 Discussion of the results for the pre-post comparison

In this second part of the phobia study, the main goal was to compare brain activations before and after the phobic subjects passed through a psychological therapy to overcome their fear. For this purpose, two experimental conditions were compared: CLEAN and PHOBIC. It was analyzed the contrast "phobic>clean" over phobic subjects for the "pre-treatment>post-treatment" and "post-treatment>pre-treatment" conditions. In the following paragraphs, those results will be commented. After that, a comparison between them and similar results obtained in other groups' work using images or videos as stimulus will be done. Finally, there will be made some overall conclusions.

Firstly, the results from the "pre-treatment>post-treatment" condition will be presented. As aforementioned, the main brain activation in this condition is set in the superior frontal lobe. That means that this is an area that was activated before the therapy (as remarked in the pre-treatment results, section 4.3.1), and this activation disappears after it. It has been discussed previously that this area is related to the feeling of self-awareness, which increases when the phobic subject watches the feared animal (Goldberg et al., 2006). The fact of this activation disappearing after the treatment supports the theory of being involved in self-awareness and proves the effectiveness of the therapy.

It has been also mentioned in the corresponding results section (section 4.3.2) the activation of the supplementary motor area (SMA), related with the control of movement. Previous works about phobias have already explained this activation due to the patients' urge to flee during a confrontation with the feared animal (Scharmüller et al., 2011). As aforementioned in the previous section, this activation accords with the embodied cognition theory (Garbarini and Adenzato, 2004), which says that observing an object activates the neural system as if you were interacting with it. So due to the fact that in this study the subjects are navigating through an environment, it makes sense that they activate the motor areas as if they were really moving. The bigger activation when a feared stimulus is present is reflected in the fact of this area not being activated after the treatment. Another group who remarked specific phobia-related activation in the supplementary motor area was Schienle et al. (2005). They studied the fear and disgust in spider phobic subjects using fMRI while alternating blocks of phobia, fear, disgust and neutral pictures. They found activation in this area while comparing the conditions "phobia>fear" and "phobia>disgust" over the phobic subjects.

Once there have been analyzed the results for this contrast, the results obtained in the "post-treatment>pre-treatment" condition will be evaluated. There were found activations in the right cerebellum, left sub-gyral temporal lobe, left thalamus, right inferior frontal gyrus, left inferior parietal lobe, left sub-gyral frontal lobe and right middle cingulum.

The main role of the cerebellum is the motor control (Grodd et al., 2001). However, it is also related with cognitive functions such as the attention and the processing of language or learning (Wolf et al., 2009). This last may be the cause of its activation, due to the learning done over the environment, which was already seen in the previous scan.

The temporal lobe is most commonly known by its relation with the auditory perception and language (Rice University, 2011). The sub-gyral activation is near the middle temporal gyrus, connected with processing of language, visual perception and multimodal sensory integration (Onitsuka et al., 2004). According to Kosslyn et al. (1996), this area is related to the vision of emotionally laden negative stimuli, result that is also coherent with the findings of Paquette et al. (2003) over control subjects. This is in accordance with the results presented here, as it was found activation in this area after the treatment, when the subject is exposed to an environment that is emotionally negative, but that does not scare him anymore.

The activation in the thalamus is related to the relay of sensory and motor signals to the cerebral cortex (Sherman, 2006). More specifically, the pulvinar area of the thalamus is associated with the sensorial stimulus integration, and has been reported to respond to visual stimulus proprieties such as orientation or direction of the movement (Petersen et al., 1985; Kastner et al., 2004). Thalamic activation has also been related with phobogenic situations previously (Straube et al., 2006; 2007). Porro et al. (2003) explained that this activation may be due to unspecific arousal response “since the midbrain reticular formation extends into the intra-laminar nuclei of the thalamus”.

The thalamus was activated after the treatment and not before, and this hypoactivation corroborates the hypothesis of Etkin et al. (2007), who stated that this may be related to a decrease in the processing of sensory information, which leads to a decrease in the experience of negative emotion. The subjects may inhibit the activation of this area to avoid the fear in the first scan, and once got over of the phobia, the activation normalizes to that of a non-phobic subject.

The right inferior frontal gyrus has been related to risk aversion responses (Christopoulos et al., 2009) and inhibition (cancel an intended movement) responses (Aron et al., 2004). This activation after the treatment is also coherent with the results obtained in

Paquette et al. (2003), where they discussed the relation of the right inferior frontal gyrus with the guidance of attention in visual space, provoking a state of "visual vigilance" devoid of emotion. Johanson et al. (2006) also found activation in the prefrontal area in panicking spiders phobic subjects after the therapy, that didn't appeared before. However, they found the contrary (increased activation before the treatment that disappeared after it) in a group of phobic subjects controlling their fear that was also included in the study. It is coherent with what has been aforementioned of this area related to inhibition responses, due to the fact that in this study it is activated when the phobic subjects are controlling their fear, that is, after the treatment.

The inferior parietal lobe has been said to play a role in the interpretation of sensory information (Radua et al., 2010). It is related to visuospatial processing and mental coordination (Purcell et al., 1998; Zielinski et al., 1991). In a study conducted by Nakao et al. (2005) using the Stroop task in fMRI with obsessive-compulsive patients before and after symptom improvement, they found parietal activation in relation to cognitive performance improvement after the treatment. The subjects from the present study would be more focused in the task and their cognitive performance would improve once the distraction caused by the fear disappears after the treatment, which would justify the observed activation in this area.

It has been also mentioned activation in the sub-gyral area of the frontal lobe, adjacent with the limbic lobe. The frontal lobe is related to executive functions like the recognition of future consequences from the current actions or to distinguish between good and bad actions; which means higher mental functions (Kimberg & Farah, 1993). Its function is related to the limbic system, involved in the emotional behavior (Papez, 1937). At last, activation was found in the right middle cingulum; that is also integrated in the limbic system, and allows the communication between its components. After the treatment the subjects are not afraid and their executive functions

are not affected by the fear, so the related areas' activation increases.

In conclusion, in this part of the study the possibilities of VR in the evaluation of phobic subjects are shown, comparing the brain activations before and after a psychological treatment to cure it. The results obtained are coherent with those from works conducted by other groups over phobic subjects using pictures or videos of real animals to elicit the fear. This finding opens the door to deeper investigations over the phobias, due to the fact that VR allows recreation of normal life scenes in a more realistic and interactive way, that are impossible to achieve with other techniques.

4.5 Overall conclusions and limitations of the study

As has been just exposed, in this study it was checked the usefulness of virtual reality in the assessment of the state and evolution of a mental distress, more specifically, in subjects with small animals' phobia. The belief was that brain areas related to the phobia that were activated before the treatment to cure the phobia, will stop being activated after that treatment. As aforementioned, one of the most important areas activated previously to the treatment was the superior frontal gyrus, related with the state of self-awareness experienced while in presence of the feared animal. This area, which was activated in the pre-treatment scan, effectively stopped being activated after the treatment.

The other area which followed this pattern of activation was the supplementary motor area. Although it did not have a significant activation in the pre-treatment scan, the difference in activation between the pre- and post-scans was significant. This area is related to the control of movement, and as Scharmüller et al. (2011) and Schienle et al. (2005) pointed out, is due to the patient's urge to flee due to the phobic stimuli; which explains the deactivation of it after the treatment.

It is also important to remark that these results are coherent with those obtained in previous studies developed using pictures of real animals as stimuli. The main activations during the pre-treatment scan were obtained in the occipital and frontal areas. In the study of Paquette et al. (2003), they found a similar activation in the former, while explained the relation of the later with the phobia (although they did not find activation in the frontal lobe, they explained this relation due to its importance in the phobia study). Apart from those, it was found activation for the "phobic>clean" contrast in the cuneus (visual processing functions) and precuneus (self-conciousness and planning of the movement). As exposed in the previous chapter (study of presence, in Chapter 3), the cuneus is an important area related to the sense of presence experienced in the virtual world. Regarding the precuneus, its activation is enhanced by the navigation in a VE.

Although the activation of the amygdala is not achieved in this study, this also goes with the conclusions obtained in previous works. As aforementioned, the amygdala suffers habituation over time (Larson et al., 2006), so its activation is only observed when studying brief periods of time (in the order of milliseconds). The use of blocks of 20s in this study may prevent us from finding activation in this area.

Moreover, during the pre-treatment scan, the activations for the "phobic>dirty" and "dirty>clean" contrasts were coherent with those obtained for the "phobic>clean". It has been already explained the choice as reference of the later contrast because it considered the results for both fear and anxiety during the virtual experience. However, it was corroborated that the results obtained in this contrast were still active when restricting the condition to avoid brain areas related to anxiety produced by the dirtiness of the room. Because the phobia maintains the patient in an alert state, the same areas are still activated when comparing the DIRTY condition with the control one (CLEAN), although this activation is less intense. In conclusion, the brain activations in the occipital and frontal areas

follow a linear trend over the experimental conditions, with a higher intensity during the PHOBIC condition and a lower but still significant activation in the DIRTY period, when comparing it with the CLEAN one.

The comparison between these three experimental conditions is also a novelty introduced by this study. Until now, for the assessment of small animals' phobias only blocks of pictures or videos of real animals had been used. The use of virtual reality allows the study of the patients' reactions in more complex situations (navigating through an environment) and in different conditions (in this case, in a dirty room with and without spiders and cockroaches). This opens the door to the study, as in this case, of patients with mild phobias, which could not be stimulated with other kind of stimuli.

Despite all the benefits that have been remarked from this study, there have also to be addressed some limitations it presents. First of all, it was conducted using a specific group of participants, namely 11 right-handed women. This constitutes a small sample size, which restricts the statistical power of the study to detect changes in the BOLD signal. All the subjects were right-handed in order to prevent noise effects due to manual lateralization on brain activation in virtual/spatial processing. Moreover, all of them were chosen women to reduce the variability generated by gender differences. In fact, some previous studies have pointed out the importance of choosing only women, due to their higher activation in presence of emotional stimuli. Canli et al. (2001) indicated that they chose women because "they report more intense emotional experiences and show more physiological reactivity in concordance with valence judgments than men". Most of the studies aforementioned have been conducted with female subjects (e.g. Paquette et al., 2003; Schienle et al., 2007; Straube et al., 2007; Scharmüller et al., 2011). Scharmüller et al. (2011) pointed out that they restricted their study to use only female subjects since the prevalence of spider phobia is higher in them. Moreover, Schienle et al. (2007) remarked that most of the spiders'

phobia sufferers were females. Another limitation could be the absence of control subjects to compare with, which could constitute a future extension of the current work. However, the use of the same group of subjects for the pre- and post- treatment scans allows the comparison between two time moments, so the same patients work as their own reference to compare with.

Because the fMRI requires the subjects to remain still, the patients to analyze were chosen with mild phobia levels, in order to avoid the possibility of them panicking during the task. This also decreases the levels of brain activation found in the study, so another future work could be the assessment of patients with higher levels of phobia, in order to corroborate the results achieved in this study.

But, what does all this mean in terms of neuropsychotherapy? This specific study was designed to validate a bigger hypothesis: that neuroimaging and VR could be combined for the benefit of the assessment process during the treatment of a patient suffering from some kind of psychological disorder. This would give the therapist wider information about his brain state and help to adjust the treatment according to this information.

In the particular example of the study of small animals' phobic subjects, the combination of neuroimaging (in this case, fMRI) and VE has given information about the brain areas that were activated related to the phobia, and how the activation patterns changed due to the treatment undergone. This information could help the psychologists that treated the subjects in further studies for the improvement of the psychological treatment according to the brain areas activated in each case. In other words, the underpinning of the areas related to a specific disorder could lead the psychologists in a better understanding of the problem and a better adjustment of its treatment.

In this case, virtual reality allows a more accurate representation of the stimuli inside the scanner, which helps in the stimulation of the

proper areas of the brain. The use of fMRI as the neuroimaging technique gives precise spatial information of the brain areas involved in the phobia, and the comparison of three experimental conditions helps in the discrimination of which brain area is related to which brain function. Combining all these, the result is a useful tool for the accurate study of the brain reaction before the small animals' phobia that will help the therapists in the better application of the psychological treatment.

5 Overall conclusions and future work

In this last chapter, the main hypothesis of this PhD Thesis will be summarized and the objectives fulfilled resumed. First, the main goals achieved in each of the two branches of study will be presented: Presence and Assessment of a treatment (small animals' phobia). Second, the publications done within the framework of this work will be presented. Finally, the future work with which the research here presented will continue will be commented.

5.1 Contributions of the present PhD Thesis

The main goal of this PhD Thesis was centered on the study of how virtual reality could be used as stimuli during neuroimaging studies to help in the underpinning of the brain areas related to specific psychological disorders, in order to use this information during the performance of the psychological treatment to improve its results (what is known as neuropsychotherapy). For this, our efforts have been centered in a specific kind of disorder (small animals' phobia) and virtual environments have been developed which can stimulate the fear in the patients. The use of VR will allow the reach of levels of exposure unable to be obtained using real stimuli. However, before being able to assure that the results here presented were related to the phobia and not to other factors that could have introduced noise in the study, it was needed to check that the subject effectively felt present inside the environments. For this, the presence study preceding to the phobia analysis was introduced. Moreover, this study helped in the decision of which neuroimaging technique (fMRI or EEG) was more suitable for accomplishing the aims of the research. According to the results from the presence study, it was chosen that the phobia study would be conducted using fMRI (see Section 3.2.5, Overall conclusions of the presence study).

From a closer point of view, both specific courses of study present novelties in their designs for their ambits of research. On the one side, the use of VR as stimuli inside the fMRI scan to assess the fear and anxiety levels in phobic subjects is a new concept that has not

yet been applied. Brain areas related to different kinds of phobias have been evaluated using fMRI, but never using virtual stimuli. The introduction of virtual environments allows the free navigation of the subject through a world more similar to the real experience than the pictures or videos normally used for this kind of researches. Moreover, it allows the modulation of the fear experience in terms of the patient's particular state, making it more suitable for his personal condition.

On the other side, the study of the sense of presence with fMRI using virtual environments through which the subject can navigate freely is something that has not been studied yet. Presence has been measured using fMRI by means of automatic navigations (videos) through virtual environments, but not allowing the subject to freely move as he would do in a real world experience. Presence during a free navigation has only been assessed using other neuroimaging technique (TCD) less precise (with a worse spatial resolution), that does not give information about the brain areas activated. In this study, the fMRI results during the presence experience were compared with those obtained using EEG, in order to provide useful information about the best technique for the measure of presence and the influence of the intrusion of the scanner in the strength of the virtual experience, in terms of brain activations.

Apart from the specific advantages that both studies present from what has been made since now regarding the research fields of presence and phobias, the thesis as a whole brings a new perspective to the assessment of the patient's brain state during the treatment of a mental disorder from a neuropsychotherapeutical point of view. In the following sections, the conclusions of both studies will be presented separately, to end with some final overall conclusions.

5.1.1 Study of Presence

In the introduction, the main hypothesis to demonstrate in this part of the study was stated. Now, each point will be analyzed separately, indicating the conclusions obtained for each one:

- Mainly, the objective was to check if the presence experience in a VE could be elicited inside a neuroimaging scan, despite the adverse conditions (such as the laid position in which the subject has to remain, or the noise emitted by the scan in the fMRI). For this, the measures acquired with two different techniques were compared: a highly intrusive one (fMRI) and a low intrusive one (portable EEG). For the fMRI study, the results obtained were in accordance with those obtained in previous works, and the areas activated were discussed as effectively being related to the presence experience. Moreover, the results of the EEG study corroborated those activations.

- In the fMRI study, the brain activations obtained for three experimental conditions were compared: photographs, video and navigation. The aim was to analyze the differences obtained when comparing situations which elicited different levels of presence. If the hypothesis stated was correct, the presence experience should be greater during the free navigation through the environment than during the video, and both greater than the visualization of photographs of the environment. As presented in the results section of the fMRI study in Chapter 3 (section 3.2.2.2.2, Imaging Results) activations were found in the cuneus, the parietal lobe and the insula (among others) for the contrast "navigation>video". Moreover, it was found an increasing linear trend in the activation between the three experimental conditions in the insula and the postcentral parietal gyrus. That means that the presence experience grows with the increase of the brain activation in these areas.

- As it was also measured the sense of presence by means of a SUS questionnaire, the fMRI results were compared with the answers given in them. It was found a negative correlation

between the presence ratings in the questionnaires and the brain activation in the DLPFC, result in accordance with those obtained in the work of Baumgartner et al. (2008).

- Then, the same study of presence was repeated using a low intrusion technique such as EEG. The aim was to measure the differences in brain activation between the same three experimental conditions. For more precision, there were compared the activations of two groups that watched the environments in two different screens: the first in a high definition Power Wall screen (EEG PW group) and the second in a PC desktop screen (EEG DS group). As detailed in the corresponding section (3.2.3.2.2, EEG Results), it was also found activation in the Insula for the alpha and theta bands for both groups, and activation in the parietal lobe for the EEG PW group.

- Then brain activations obtained from both techniques were compared, concluding that they were similar (despite the differences in spatial resolution between the techniques). With this, it was agreed that the sense of presence was excited with both neuroimaging techniques and that the virtual experience was strong enough to be used to measure phobias in the next part of the study.

- Thanks to the questionnaire results, it was checked that the subjective ratings of the presence experience were in fact similar, and no significant differences were found between techniques, while there were between experimental conditions.

- As an extra objective, the usefulness of the Emotiv EPOC for the research field was studied. This headset, although designed for more commercial applications such as games,

could save time and money if demonstrated its functioning in the research area. Not only this device costs far less than any other neuroimaging scan, but also its placement over the scalp takes only a few minutes, in comparison with the half an hour needed for other EEG devices. The good results obtained in this work encourage the belief that the Emotiv EPOC can be a suitable alternative to more expensive and complicated techniques when the situation requires it.

- Finally, all this information allowed the choice of the neuroimaging technique to use in the second part of the work. All the facts considered, it was decided the use of fMRI in the "assessment of a treatment" study, due to its better spatial resolution.

In addition to the hypothesis presented in the Introduction, which have all been proved, the results of the study validated the hypothesis of the Human Computer Interaction theory: the interaction between the computer-generated world and the subject is naturally performed, and that leads to the reduction of the barrier existing between technology and reality. As aforementioned, finding the neural correlates hidden behind the sense of presence will help in the development of adaptative Brain-Computer Interfaces. The future of virtual reality will be the control of the environments using the brain signals directly, if you are able to distinguish among the brain areas involved in the virtual experience. For that, it is necessary the vanishing of technology from the user's awareness, what Riva et al. (2003) call "disappearance of mediation". This study is a small step towards this objective, showing the usefulness of neuroimaging techniques for the distinction of the brain areas related to the sense of presence and the possibility of differentiating the presence experienced under different experimental conditions.

5.1.2 Study Assessment of a Treatment: Small Animals' Phobia

In this section the objectives established for this part of the Thesis and the level of accomplishment of them will be reviewed.

- First of all, the objective was to obtain the brain areas related to the small animals' phobia during three conditions: clean, dirty and phobic. Those results correspond to those obtained in the pre-treatment fMRI scan. As explained in the Chapter 4 (section 4.3.1), activation was found mainly in the inferior occipital lobe and superior frontal gyrus for the "phobic>clean" contrast. The activations in the occipital and frontal lobes were still present during the dirty condition, although in a milder level, because of the anxiety caused by the dirtiness of the room.

- Those activations were compared with the ones obtained in previous researches conducted by other groups, using real animals as stimulus. As explained in the corresponding discussion (section 4.4.1), the activation in the occipital lobe is related to enhanced visual attention to the phobic stimuli (Paquette et al., 2003) and the superior frontal gyrus is related to self-awareness (Goldberg et al., 2006), which is increased when the phobic subject watches the animal that provokes his fear. Effectively, those results are in accordance with those obtained in previous works. Moreover, the no activation in the amygdala is due to the habituation over time (Larson et al., 2006). Because of the use in this work of periods of time to study the phobia instead of event-related fMRI, this area did not appear in the results; but this result is also in coherence with what previous researches stated.

- The third goal was to obtain the brain areas activated in the subjects after the psychological treatment, once their phobia was gone (contrast "phobic>clean"). For the "pre-treatment

> post-treatment" contrast, it was obtained that the superior frontal gyrus, that was activated before the treatment, stopped being activated after it (section 4.3.2 of the Chapter 4).

- Finally, there were areas which activation was inhibited because of the phobia, and once it was cured, their activation was restored ("post-treatment>pre-treatment" contrast's results).

In conclusion, the results obtained were in concordance with those from previous researches developed using real animals as stimuli, and fulfilled the initial objectives that had been established. The activations of the brain areas related to the phobia disappeared after the treatment (specially the activation in the superior frontal gyrus), and the areas with activity that was inhibited because of the phobia returned to their normal working once the therapy was completed.

5.1.3 Final Overall Conclusions

Despite all that has been stated before, the main goal of this whole study was to analyze if VR could be used as a stimuli during a neuroimaging scan for the assessment of the mental state of a patient undergoing a psychological treatment, and if this could bring useful information for the modulation of the therapeutic process.

The presence study allowed measuring the strength of the virtual experience, at the same time as it helped in the choice of the more suitable neuroimaging technique. The Assessment of a treatment study informed about the possibilities of using neuroimaging and VR for the study of the neuroplasticity of the brain. All this considered, it was concluded that the combination of both techniques could bring important information in the assessment of patients with mental disorders.

Effectively, the results are encouraging and show that VR and neuroimaging can be important allies in the underpinning of the

brain areas related to each specific disorder. This could lead in the future to important progresses in the neuropsychotherapy science.

5.2 Publications

In this section, the publications derived from this PhD Thesis will be presented. In total, there are 2 papers accepted in journals in the JCR Science Edition, four presentations in international conferences (3 oral presentations and one poster) and 3 posters presented in national conferences. Two of the oral presentations were also published in the form of book chapters and from the other a full length article was derived. The poster presented in an international conference was a Core A. Finally, the PhD Project won the Valencia IDEA award.

5.2.1 Publications in journals included in the JCR Science Edition

- Miriam Clemente, Beatriz Rey, Aina Rodríguez-Pujadas, Alfonso Barros-Loscertales, Rosa M. Baños, Cristina Botella, Mariano Alcañiz, and César Ávila. (2013). An fMRI Study to Analyze Neural Correlates of Presence during Virtual Reality Experiences. Interacting with Computers.
  DOI: 10.1093/iwc/iwt037

  In this work, the results of the presence study using fMRI were presented. The journal had an impact factor of 1.158 in 2012 and was indexed in the second quartile of the Computer Science, Cybernetics category.

- Miriam Clemente, Alejandro Rodríguez, Beatriz Rey, and Mariano Alcañiz. (2013). Assessment of the influence of navigation control and screen size on the sense of presence in virtual reality using EEG. Expert Systems with Applications.
  DOI: http://dx.doi.org/10.1016/j.eswa.2013.08.055

In this work, the results of the presence study using EEG for the comparison between the brain activations obtained when comparing different navigation conditions and screen sizes with the Emotiv EPOC headset were presented. The journal had an impact factor of 1.854 in 2012 and was indexed in the first quartile of the categories Engineering, Electrical & Electronic and Operations Research & Management Science, and in the second quartile of the Computer Science, Artificial Intelligence category.

Apart from those papers, a third one has been sent about the results regarding the comparison pre-post in the phobia study, the resolution of which has not been released yet.

5.2.2 Book chapters - Conference proceedings

- Miriam Clemente, Beatriz Rey, Mariano Alcañiz, Juani Bretón-López, Inés Moragrega, Rosa M. Baños, Cristina Botella, and César Ávila. (2010). Contributions of functional Magnetic Resonance in the field of Psychological Treatments with Virtual Reality. Studies in Health Technology and Informatics 154, pp. 197-201.
  DOI: 10.3233/978-1-60750-561-7-197

  This work was presented as an oral communication in the 15th annual CyberPsychology and CyberTherapy 2010 Conference, held in Seoul (Korea), 13-15th June 2010. It introduced the experimental design of the phobia branch of study of this PhD Thesis.

- Miriam Clemente, Alejandro Rodríguez, Beatriz Rey, Aina Rodríguez, Rosa M. Baños, Cristina Botella, Mariano Alcañiz, and César Ávila. (2011). Analyzing the Level of Presence While Navigating in a Virtual Environment during an fMRI Scan. INTERACT 2011, Part IV, LNCS 6949, pp. 475–478.

This work was presented as a poster in the 2011 Conference on Human-Computer Interaction, held in Lisbon (Portugal), 5-9 September 2011. This congress is included in the Computing Research and Education Association of Australasia (CORE) list in the A category. It presented the preliminary results of the presence study using fMRI and the questionnaire results' comparison with the TCD study.

- Miriam Clemente, Beatriz Rey, Mariano Alcañiz, Juani Bretón-López, Cristina Botella, Aina Rodríguez-Pujadas, Alfonso Barros-Loscertales, César Ávila and Rosa M. Baños. (2013). fMRI assessment of small animals' phobia using virtual reality as stimulus.

  This work was presented as an oral presentation in the 1st Patients Rehabilitation Research Techniques Workshop (REHAB 2013), held in Venice (Italy), the 5th of May of 2013. It presented the results for the pre-treatment brain activations obtained in the phobia study using fMRI. The extended results of this part of the study were sent to the special issue derived from the conference; the resolution has not been released yet.

- Miriam Clemente, Alejandro Rodríguez, Beatriz Rey, and Mariano Alcañiz. (2013). Measuring presence during the navigation in a Virtual Environment using EEG. Studies in Health Technology and Informatics 191, pp. 136-140.
  DOI: 10.3233/978-1-61499-282-0-136.

  This work was presented as an oral presentation in the 18th annual CyberPsychology and CyberTherapy 2013 Conference, held in Brussels (Belgium), 30th June- 2nd July 2013. It presented the preliminary results for the EEG study of

presence using the Emotiv EPOC headset with a PC desktop screen.

5.2.3 Other conference presentations

- Miriam Clemente, Beatriz Rey, Mariano Alcañiz, Rosa M. Baños, Cristina Botella and César Ávila. (2010). Uso de la resonancia magnética funcional y estímulos de realidad virtual para evaluación de fobia a animales pequeños.

  This work was presented as a poster in the XI Congreso Multimodalidad ADIRM 2010 - Trastornos psiquiátricos: relaciones, conexiones y alteraciones, held in Valencia (Spain), 14th of December of 2010.

- Miriam Clemente, Beatriz Rey, and Mariano Alcañiz. (2011). Analyzing spatial memory with fMRI using a virtual reality version of a real city.

  This work was presented as a poster in the International Symposium on Learning, Memory and Cognitive Function 2011, held in Valencia (Spain), 1st - 3rd December 2011.

- Miriam Clemente, Beatriz Rey, and Mariano Alcañiz. (2011). Aplicaciones del uso combinado de neuroimagen con realidad virtual.

  This work was presented as a poster in the VIII Congreso de la Sociedad Española de Psicofisiología y Neurociencia Cognitiva y Afectiva (SEPNECA), held in Barcelona (Spain), 3 – 6th July 2012.

5.2.4 Awards

The project in which this PhD Thesis is based won the first prize in the category "Biotecnología y Biomedicina" of the 5th Valencia IDEA award in 2011.

5.3 Future work

After the good results obtained using EEG for the measure of brain activity, the corresponding part of the thesis will be augmented. The idea is, on one side, increase the number of subjects in both groups studies with the Emotiv EPOC headset for the study of presence, in order to increase the significance of the results. On the other side, it is intended to replicate the study using a more precise EEG devise, a little more invasive but at the same time with a better resolution (such as the TMSi headset (TMS International BV, Oldenzaal, The Netherlands)). Moreover, another study will be developed for the study of the "breaks in presence" during a virtual reality experience, also using EEG. The first data for this study have been already obtained.

Regarding the study of phobias, the present work will be replied using EEG to compare the results obtained with this technique with the ones already presented in this PhD Thesis. Moreover, the study will be replied using non-phobic subjects, to check if the areas related to the phobia are not activated in them.

The hypothesis of this PhD about the contributions to neuropsychotherapy will also be analyzed with another psychological case study, to check if the same conclusions can be deduced.

In the following points some of the future lines of study that will be derived from this thesis are related:

- In the present PhD Thesis, good results for the study of presence were obtained with both neuroimaging techniques. The number of subjects for the EEG study (10 for each kind of screen, 20 in total) is limited. As aforementioned, enlarging

the list of subjects will increase the significance of the results, and probe the validity of the conclusions.

- One special branch of research inside the analysis of presence in virtual reality is the study of “breaks in presence” or BIPs. For this purpose, a virtual environment was developed in the LabHuman laboratory, using Doppler for the measure of the brain. Another line of work will be to reproduce the study of BIPs already done with TCD using EEG (both TMSi and Emotiv EPOC headsets). The study will also analyze the differences due to the screen sizes, using both the desktop PC screen and the Power Wall. This research has already begun. It has been already acquired the data from 40 subjects (also 10 per each screen and device), and they will be analyzed soon.

- Regarding the study of phobias, the study was successful using fMRI for the analysis of phobic subjects. In a future line of work, it would be interesting to reply the same experimental design using EEG to check if the results obtained are the same as with the fMRI scanner. This would bring useful information about the temporal evolution of the brain areas activated in each moment of the phobic exposure, and for example, show the brief activation of the amygdala (according to what was explained in the corresponding discussion of the results).

- Another possible study could be the analysis of the brain areas activated with the same virtual environments in non-phobic subjects, to check that the areas that were considered related to the phobia are not activated in them.

- A long-term post-treatment analysis of the phobic subjects from the fMRI study could also be done to corroborate that

the brain areas related to the phobia are still not activated and that the subject remains cured.

- In a combined work with the psychologists involved in this work, the application of the obtained information to the treatment of small animals' phobic subjects will be evaluated, allowing the therapists to provide a treatment based on the knowledge of brain activations, in order to contribute to the neuropsychotherapy.

The principal objective in this PhD Thesis was to probe the usefulness of the new neuroimaging techniques and the goodness of combining them with virtual reality stimulus. In the future, the line of work to follow will continue in the analysis of possible applications of neuroimaging (especially fMRI and EEG) using virtual environments. In this sense, several projects have already been proposed; that are expected to result in satisfying conclusions for the matter:

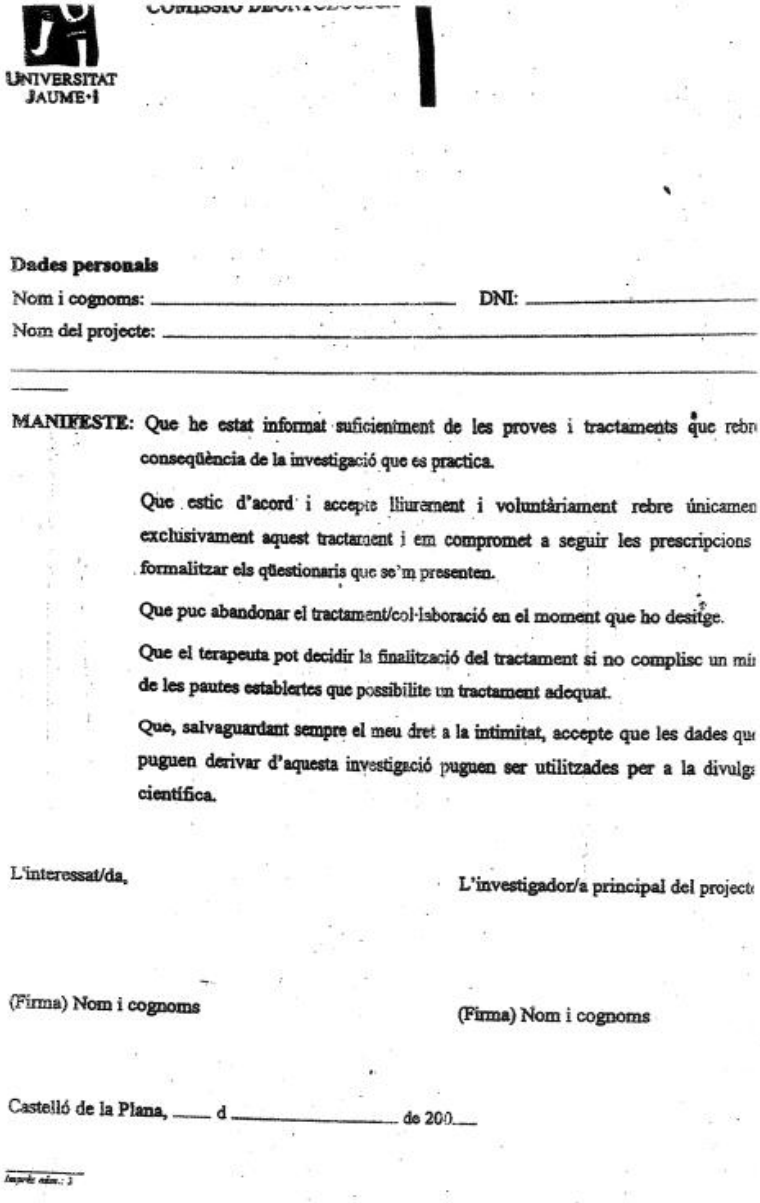
- **Evaluation of the results of a cognitive treatment over Acquired Brain Injury (ABI) patients, using fMRI and DTI.** In this study, ABI patients will be studied before and after passing through a new kind of cognitive treatment developed using virtual reality games. During the scans, the subjects will attend attention tasks similar to those conducted during the treatment. The objective will be to probe the goodness of this new kind of treatment and to study the plasticity of the brain.
- **Evaluation of the results of a motor treatment over Acquired Brain Injury (ABI) patients, using fMRI and DTI.** Similarly to the previous study, in this one ABI patients will be analyzed before and after passing through a new kind of motor treatment, also developed using virtual reality games. During the scans, the subjects will perform several motor tasks with the upper limbs (wrist and elbow) with both the affected and the healthy member. The objective in this case

will be also to probe the goodness of this new kind of treatment and to study the plasticity of the brain, this time for the motor areas.

6 Appendixes

Appendix 1

Informed consent to sign before entering the fMRI scan



UNIVERSITAT JAUME·I

Dades personals

Nom i cognoms: _____ DNI: _____

Nom del projecte: _____

_____

_____

MANIFESTE: Que he estat informat suficientment de les proves i tractaments que rebr conseqüència de la investigació que es practica.

Que estic d'acord i accepte lliurement i voluntàriament rebre únicamen exclusivament aquest tractament i em compromet a seguir les prescripcions formalitzar els qüestionaris que se'm presenten.

Que puc abandonar el tractament/col·laboració en el moment que ho desitge.

Que el terapeuta pot decidir la finalització del tractament si no complisc un mí de les pautes establertes que possibilite un tractament adequat.

Que, salvaguardant sempre el meu dret a la intimitat, accepte que les dades qu puguen derivar d'aquesta investigació puguen ser utilitzades per a la divulg científica.

L'interessat/da,

L'investigador/a principal del projecte

(Firma) Nom i cognoms

(Firma) Nom i cognoms

Castelló de la Plana, ____ d _____ de 200__

Appendix 2

Informed consent to sign before passing the EEG scan

DATOS PERSONALES:

Nombre y apellidos:

DNI:

Edad:

Nombre del proyecto: Presencia EEG y BIPs EEG

MANIFIESTO:

- Que he estado suficientemente informado de las pruebas que recibiré a consecuencia de la investigación que se practica.
- Que estoy de acuerdo y acepto libre y voluntariamente participar exclusivamente en esta prueba, y me comprometo a seguir las instrucciones y formalizar los cuestionarios que se me presenten.
- Que he sido informado suficientemente de la utilización de las señales de EEG-Emotiv que se monitorizarán durante la prueba.
- Que, salvaguardando siempre mi derecho a la intimidad y al anonimato, estoy de acuerdo y acepto libre y voluntariamente la captura de mis señales de EEG durante la participación en la prueba.
- Que puedo abandonar la prueba en el momento que lo desee.
- Que, guardando siempre mi derecho a la intimidad, acepto que los datos que puedan derivarse de esta investigación puedan utilizarse para la divulgación científica.

El interesado — El investigador principal del proyecto

(Firma) — (Firma)

Valencia, _____ de _____ de 201_

Appendix 3

Edinburgh Handedness Inventory questionnaire (Oldfield et al., 1971)

This questionnaire measures the laterality (if they are left or right handed) over the participants of the study. It's worthy to remember that in this study it were used right-handed subjects, in order to obtain equivalent brain activations regarding the dominant hemisphere of the brain (in the right-handed people, the dominant side is the left hemisphere; however, between the left-handed people there is no fixed dominant side).

EDINBURGH HANDEDNESS INVENTORY

(Oldfield, 1971; Bryden, 1977)

Nombre: Varón [ ] Mujer [ ]
Fecha: F. nacimiento: Edad:
Estudios/Profesión: Observaciones:

INSTRUCCIONES: *Marque la casilla correspondiente con*

+ *una cruz, si es la mano que utiliza de modo preferente.*
++ *dos cruces, si es la mano que utiliza de modo muy preferente y además le resultaría imposible o muy difícil hacerlo con la otra mano.*
+ *una cruz, en las dos casillas cuando pueda hacerlo tan bien tanto con una mano como con la otra.*

¿QUÉ MANO UTILIZA PARA?	DERECHA	IZQUIERDA	Puntos
1. Escribir			1-2-3-4-5
2. Dibujar			1-2-3-4-5
3. Lanzar un objeto			1-2-3-4-5
4. Limpiarse los dientes			1-2-3-4-5
5. Utilizar un cuchillo (sin tenedor)			1-2-3-4-5
6. Cortar con tijeras			1-2-3-4-5
7. Comer con la cuchara			1-2-3-4-5
8. La mano que coloca en la parte superior de la escoba para barrer			1-2-3-4-5
9. Rascar una cerilla			1-2-3-4-5
10. Levantar la tapa de una caja			1-2-3-4-5

Appendix 4

SUS Questionnaires (Usoh et al., 2000)

In this appendix, there will be presented the SUS questionnaires (Usoh et al., 2000) used for the subjective measure of presence, personalized for each of the experimental conditions: photographs, video and navigation.

VALORACIÓN DE LA HABITACIÓN DURANTE EL VISIONADO DE FOTOGRAFÍAS

INICIALES……..…. FECHA DE NACIMIENTO……..…

A continuación te vamos a hacer una serie de preguntas. El objetivo es saber hasta qué punto has considerado real o no las cosas que has visto, y hasta qué punto has sentido que "tú estabas ahí", en esa situación. Queremos saber hasta qué punto la experiencia ha sido parecida a ver una imagen o una película de cine, o ha sido la realidad que estabas viviendo.

1. Por favor, valora la sensación que has tenido de estar en la habitación, en una escala de 1 a 7 (donde 7 representa tu experiencia normal de estar en un lugar).
Tuve la sensación de "estar ahí", en la habitación.
1 Nada en absoluto..... 7 Totalmente

1	**2**	**3**	**4**	**5**	**6**	**7**

2. Por favor, valora en una escala de 1 a 7 si hubo momentos durante la experiencia en los que creíste que la habitación era real
Hubo momentos durante la experiencia en que la habitación era real para mí.
1 En ningún momento, siempre me pareció totalmente irreal.....7 Me pareció real todo el tiempo

1	**2**	**3**	**4**	**5**	**6**	**7**

3. Ahora, al reflexionar y pensar sobre la experiencia que has vivido, ¿cómo recuerdas la habitación, como una

imagen (una película, una foto) que has visto, o como un sitio en el que tú has estado

Al pensar en la habitación, lo recuerdo más como…

1 Imágenes que he visto..... 7 Como un sitio en el que he estado

1	**2**	**3**	**4**	**5**	**6**	**7**

4. Mientras duraba esta experiencia, lo que has sentido con más fuerza es que estabas "en la habitación", o has sentido que estabas en otro sitio viendo la imagen de una habitación

Mi mayor sensación fue la de...

1 Estar en otro sitio viendo la imagen.....7 Estar en la habitación

1	**2**	**3**	**4**	**5**	**6**	**7**

5. Piensa en el recuerdo que tienes de estar en "la habitación" ¿Hasta qué punto ese recuerdo es similar a otros recuerdos que tienes de haber estado en otros sitios parecidos? (Considera cosas tales como: el grado de ese recuerdo, su color, si es vívido o realista, su tamaño, su localización en tu imaginación, etc.)

1. Totalmente distinto..... 7. Completamente igual.

1	**2**	**3**	**4**	**5**	**6**	**7**

6. Mientras duró la experiencia, solías pensar que tú estabas realmente en la habitación que se te mostraba.

Durante la experiencia, solía pensar que estaba en la habitación.

1 Nunca..... 7 Todo el rato

1	2	3	4	5	6	7

7. Por favor, escribe cualquier comentario que quieras sobre la experiencia. Especialmente todo aquello que te ayudó a sentir que estabas en una habitación y que era real.

VALORACIÓN DE LA HABITACIÓN DURANTE EL VISIONADO DE VÍDEOS

INICIALES…… FECHA DE NACIMIENTO……..…

A continuación te vamos a hacer una serie de preguntas. El objetivo es saber hasta qué punto has considerado real o no las cosas que has visto, y hasta qué punto has sentido que "tú estabas ahí", en esa situación. Queremos saber hasta qué punto la experiencia ha sido parecida a ver una imagen o una película de cine, o ha sido la realidad que estabas viviendo.

1. Por favor, valora la sensación que has tenido de estar en la habitación, en una escala de 1 a 7 (donde 7 representa tu experiencia normal de estar en un lugar).
Tuve la sensación de "estar ahí", en la habitación.
1 Nada en absoluto..... 7 Totalmente

1	**2**	**3**	**4**	**5**	**6**	**7**

2. Por favor, valora en una escala de 1 a 7 si hubo momentos durante la experiencia en los que creíste que la habitación era real
Hubo momentos durante la experiencia en que la habitación era real para mí.
1 En ningún momento, siempre me pareció totalmente irreal.....7 Me pareció real todo el tiempo

1	**2**	**3**	**4**	**5**	**6**	**7**

3. Ahora, al reflexionar y pensar sobre la experiencia que has vivido, ¿cómo recuerdas la habitación, como una

imagen (una película, una foto) que has visto, o como un sitio en el que tú has estado

Al pensar en la habitación, lo recuerdo más como…

1 Imágenes que he visto..... 7 Como un sitio en el que he estado

1	2	3	4	5	6	7

4. Mientras duraba esta experiencia, lo que has sentido con más fuerza es que estabas "en la habitación", o has sentido que estabas en otro sitio viendo la imagen de una habitación

Mi mayor sensación fue la de...

1 Estar en otro sitio viendo la imagen.....7 Estar en la habitación

1	2	3	4	5	6	7

5. Piensa en el recuerdo que tienes de estar en "la habitación" ¿Hasta qué punto ese recuerdo es similar a otros recuerdos que tienes de haber estado en otros sitios parecidos? (Considera cosas tales como: el grado de ese recuerdo, su color, si es vívido o realista, su tamaño, su localización en tu imaginación, etc.)

1. Totalmente distinto..... 7. Completamente igual.

1	2	3	4	5	6	7

6. Mientras duró la experiencia, solías pensar que tú estabas realmente en la habitación que se te mostraba.

Durante la experiencia, solía pensar que estaba en la habitación.

1 Nunca..... 7 Todo el rato

1	2	3	4	5	6	7

7. Por favor, escribe cualquier comentario que quieras sobre la experiencia. Especialmente todo aquello que te ayudó a sentir que estabas en una habitación y que era real.

VALORACIÓN DE LA HABITACIÓN DURANTE LA NAVEGACIÓN

INICIALES…… FECHA DE NACIMIENTO……..…

A continuación te vamos a hacer una serie de preguntas. El objetivo es saber hasta qué punto has considerado real o no las cosas que has visto, y hasta qué punto has sentido que "tú estabas ahí", en esa situación. Queremos saber hasta qué punto la experiencia ha sido parecida a ver una imagen o una película de cine, o ha sido la realidad que estabas viviendo.

1. Por favor, valora la sensación que has tenido de estar en la habitación, en una escala de 1 a 7 (donde 7 representa tu experiencia normal de estar en un lugar).
Tuve la sensación de "estar ahí", en la habitación.
1 Nada en absoluto..... 7 Totalmente

1	**2**	**3**	**4**	**5**	**6**	**7**

2. Por favor, valora en una escala de 1 a 7 si hubo momentos durante la experiencia en los que creíste que la habitación era real
Hubo momentos durante la experiencia en que la habitación era real para mí.
1 En ningún momento, siempre me pareció totalmente irreal.....7 Me pareció real todo el tiempo

1	**2**	**3**	**4**	**5**	**6**	**7**

3. Ahora, al reflexionar y pensar sobre la experiencia que has vivido, ¿cómo recuerdas la habitación, como una

imagen (una película, una foto) que has visto, o como un sitio en el que tú has estado

Al pensar en la habitación, lo recuerdo más como…

1 Imágenes que he visto..... 7 Como un sitio en el que he estado

1	**2**	**3**	**4**	**5**	**6**	**7**

4. Mientras duraba esta experiencia, lo que has sentido con más fuerza es que estabas "en la habitación", o has sentido que estabas en otro sitio viendo la imagen de una habitación

Mi mayor sensación fue la de...

1 Estar en otro sitio viendo la imagen.....7 Estar en la habitación

1	**2**	**3**	**4**	**5**	**6**	**7**

5. Piensa en el recuerdo que tienes de estar en "la habitación" ¿Hasta qué punto ese recuerdo es similar a otros recuerdos que tienes de haber estado en otros sitios parecidos? (Considera cosas tales como: el grado de ese recuerdo, su color, si es vívido o realista, su tamaño, su localización en tu imaginación, etc.)

1. Totalmente distinto..... 7. Completamente igual.

1	**2**	**3**	**4**	**5**	**6**	**7**

6. Mientras duró la experiencia, solías pensar que tú estabas realmente en la habitación que se te mostraba.

Durante la experiencia, solía pensar que estaba en la habitación.

1 Nunca..... 7 Todo el rato

1	2	3	4	5	6	7

7. Por favor, escribe cualquier comentario que quieras sobre la experiencia. Especialmente todo aquello que te ayudó a sentir que estabas en una habitación y que era real.

Appendix 5

The diagnostic criteria (DSM-IV) for 300.29 specific phobia.

Diagnostic criteria for 300.29 Specific Phobia

A. Marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

B. Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally bound or situationally predisposed Panic Attack. **Note:** In children, the anxiety may be expressed by crying, tantrums, freezing, or clinging.

C. The person recognizes that the fear is excessive or unreasonable. **Note:** In children, this feature may be absent.

D. The phobic situation(s) is avoided or else is endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The anxiety, Panic Attacks, or phobic avoidance associated with the specific object or situation are not better accounted for by another mental disorder, such as Obsessive-Compulsive Disorder (e.g., fear of dirt in someone with an obsession about contamination), Posttraumatic Stress Disorder (e.g., avoidance of stimuli associated with a severe stressor), Separation Anxiety Disorder (e.g., avoidance of school), Social Phobia (e.g., avoidance of

social situations because of fear of embarrassment), Panic Disorder With Agoraphobia, or Agoraphobia Without History of Panic Disorder.

Specify type:

Animal Type

Natural Environment Type (e.g., heights, storms, water)

Blood-Injection-Injury Type

Situational Type (e.g., airplanes, elevators, enclosed places)

Other Type (e.g., fear of choking, vomiting, or contracting an illness; in children, fear of loud sounds or costumed characters)

Appendix 6

The Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV) for the specific phobias.

In this appendix it is presented a semi-structured model of interview for the assessment of the phobia.

SPECIFIC PHOBIA

I. INITIAL INQUIRY

For each situation, make separate ratings for level of fear and degree of avoidance using the following scale:

0----------1----------2----------3----------4----------5----------6----------7----------8

No fear/ Mild fear/ Moderate fear/ Severe fear/ Very severe fear/
Never avoids Rarely avoids Sometimes avoids Often avoids Always avoids

For each situation, inquire for both current and past episodes:

1. **Currently, do you fear or feel a need to avoid such things as:**
Use space for comments to record other clinically useful information (e.g., frequency with which feared situation arises).

	FEAR	AVOID	COMMENTS
a. Animals (e.g., snakes, spiders, dogs, bees/insects)	___	___	_____
b. natural Environment			
Heights	___	___	_____
Storms	___	___	_____
Water	___	___	_____
c. Blood/injection/injury: self			
Blood from minor cut	___	___	_____
Receiving injections	___	___	_____
Having blood drawn	___	___	_____

d. Blood/injection/injury: others

Blood from minor cut	___	___	_____
Receiving injections	___	___	_____
Having blood drawn	___	___	_____

e. Situational

Air travel	___	___	_____
Elevators/ small enclosed places	___	___	_____
Driving	___	___	_____

f. Other

Dental/medical procedures	___	___	_____
Choking	___	___	_____
Vomiting			
Contracting an illness			

****

If no evidence is found for fear/avoidance, skip to PTSD

****

II. CURRENT EPISODES

Complete for each specific fear that is potentially of clinical severity:

Now I want to ask you a series of questions about your <u>current</u> specific fears.

A. Specific fear #1:

_____

_____

1. **What are you concerned will happen in this situation?**

_____

_____

_____

2. **Do you experience the anxiety nearly every time you encounter _____?**

YES ____ NO ____

3. **Does the anxiety occur as soon as you enter the situation or are about to enter the situation, or is the anxiety sometimes delayed or unexpected?**

IMMEDIATE ____ DELAYED ____

4a. **Are you anxious about this situation because you are afraid that you will have an unexpected panic attack?**

YES ____ NO ____

If YES,

b. **Other than times when you are exposed to _____, have you experienced an unexpected rush of fear/anxiety?**

YES ____ NO ____

If YES, **where has this occurred?**

_____

If YES to 4a. or 4b., consider whether fear could be subsumed into panic disorder.

5. Panic Attack Symptoms

Do you experience _____ when you encounter _____?

0----------1----------2----------3----------4----------5----------6----------7----------8

None Mild Moderate Severe Very severe

a. Palpitations, pounding heart, or accelerated heart rate	___	i. Dizziness, unsteady feelings, lightheadedness, or faintness	___
b. Sweating	___	j. Feeling of unreality or being detached from oneself	___
c. Trembling or shaking	___	k. Numbing or tingling sensations	___
d. Shortness of breath or smothering sensations	___	l. Fear of dying	___
e. Feeling of choking	___	m. Fear of going crazy	
f. Chest pain or discomfort	___	n. fear of doing something	
g. Nausea or stomach			

distress uncontrolled
h. Chills, hot flushes, or blushing

6. **In what ways has this fear interfered with your life (e.g., daily routine, job, social activities)? How much are you bothered by this fear?**

_____
_____
_____

Rate interference: _____ distress: _____

0----------1----------2----------3----------4----------5----------6----------7----------8

None Mild Moderate Severe Very severe

7a. **When did the anxiety about _____ begin to be a problem in that it caused a lot of distress or interfered with your life?** (Note: if patient is vague in date of onset, attempt to ascertain more specific information, e.g., by linking onset to objective life events)

_____
_____
Date of Onset: _____ Month _____ Year

b. **Can you recall anything that might have led to this fear?**

_____
_____
_____

B. Specific fear #2:

_____
_____

1. **What are you concerned will happen in this situation?**

_____

_____

_____

2. **Do you experience the anxiety nearly every time you encounter _____?**

YES ____ NO ____

3. **Does the anxiety occur as soon as you enter the situation or are about to enter the situation, or is the anxiety sometimes delayed or unexpected?**

IMMEDIATE ____ DELAYED ____

4a. **Are you anxious about this situation because you are afraid that you will have an unexpected panic attack?**

YES ____ NO ____

If YES,

b. **Other than times when you are exposed to _____, have you experienced an unexpected rush of fear/anxiety?**

YES ____ NO ____

If YES, **where has this occurred?**

_____

If YES to 4a. or 4b., consider whether fear could be subsumed into panic disorder.

5. Panic Attack Symptoms

Do you experience _____ when you encounter _____?

0----------1----------2----------3----------4----------5----------6----------7----------8

None Mild Moderate Severe Very severe

a. Palpitations, pounding heart, or accelerated heart rate ___
b. Sweating ___
c. Trembling or shaking ___
d. Shortness of breath or smothering sensations ___
e. Feeling of choking ___
f. Chest pain or discomfort ___
g. Nausea or stomach distress
h. Chills, hot flushes, or blushing
i. Dizziness, unsteady feelings, lightheadedness, or faintness ___
j. Feeling of unreality or being detached from oneself ___
k. Numbing or tingling sensations ___
l. Fear of dying ___
m. Fear of going crazy
n. fear of doing something uncontrolled

6. **In what ways has this fear interfered with your life (e.g., daily routine, job, social activities)? How much are you bothered by this fear?**

_____
_____
_____

Rate interference: _____ distress: _____

0----------1----------2----------3----------4----------5----------6----------7----------8

None Mild Moderate Severe Very severe

7a. **When did the anxiety about _____ begin to be a problem in that it caused a lot of distress or interfered with your life?** (Note: if patient is vague in date of onset, attempt to ascertain more specific information, e.g., by linking onset to objective life events)

_____
_____

Date of Onset: _____ Month _____ Year

b. **Can you recall anything that might have led to this fear?**

_____

_____

_____

7 List of Figures

8 List of Tables

9 Bibliography

Aggleton, J. P. (1993). The contributions of the amygdala to normal and abnormal emotional states. TINS, 16, 328-333.

Aguirre, G.K., Detre, J.A., Alsop, D.C., & D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. Cereb Cortex, 6, 823-829. doi:10.1093/cercor/6.6.823.

Alcañiz, M., Rey, B., Tembl, J., & Parkhutik, V. (2009). A neuroscience approach to virtual reality experience using transcranial Doppler monitoring. Presence, 18, 97-111.

Alcañiz, M., Perpiña, C., Baños, R., Lozano, J., Montesa, J., Botella, C., Palacios, A., Villa, H., & Lozano, J. (2000). A New Realistic 3D Body Representation in Virtual Environments for the Treatment of Disturbed Body Image in Eating Disorders. CyberPsychology & Behavior, 3, 433-439.

Alpers, G.W., Gendes, A.B.M., Lagarie, B., Tabbert, K., Vailt, D., & Stark, R. (2009). Attention and amygdala activity: an fMRI study with spider pictures in spider phobia. J Neural Transm, 116, 747-757.

Amaro Jr, E., & Barker, G. J. (2006). Study design in fMRI: Basic principles. Brain and cognition, 60(3), 220-232.

American Psychiatric Association. (2000). Diagnostic and Statistical Manual of Mental Disorders. 4th ed., text revision. Washington, DC: American Psychiatric Association.

Arntz, A., Lavy, E.,Van Den Berg, G., & Van Rijsoort, S. (1993). Negative beliefs of spider phobics: A psychometric evaluation of the spider phobia beliefs questionnaire. Advances in Behaviour Research and Therapy, 15, 257–277.

Aron, A.R., Robbins, T.W., & Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. TRENDS in cognitive sciences, 8, 170-177.

Astafiev, S.V., Stanley, C.M., Shulman, G.L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. Nature Neuroscience, 7, 542-548.

Astur, R. S., Germain, S. A., Baker, E. K., Calhoun, V., Pearlson, G. D., & Constable, R. T. (2005). fMRI hippocampal activity during a VirtualRadial arm maze. Applied psychophysiology and biofeedback 30: 307–317.

Bandettini P.A., Wong E.C., Hinks R.S., Tikofsky R.S. & Hyde J.S. (1992). Time course EPI of human brain function during task activation Magn. Res. Med. 25, 390-397.

Baños, R. M., Botella, C., García-Palacios, A., Villa, H., Perpiñá, C., & Alcañiz, M. (2000). Presence and reality judgment in virtual environments: A unitary construct? CyberPsychology & Behavior 3: 327–335.

Baños, R.M., Guillen, V., Quero, S., García-Palacios, A., Alcañiz, M., & Botella, C. (2011). A virtual reality system for the treatment of stress-related disorders: A preliminary analysis of efficacy compared to a standard cognitive behavioral program. Int J Human-Computer Studies, 69, 602-613.

Baumann, S., Neff, C., Fetzick, S., Stangl, G., Basler, L., Vereneck, R., & Schneider, W. (2003). A virtual reality system for neurobehavioral and functional MRI studies. CyberPsychology & Behavior 6: 259–266. doi:10.1089/109493103322011542.

Baumgartner, T., Speck, D., Wettstein, D., Masnari, O., Beeli, G., & Jäncke, L. (2008). Feeling present in arousing virtual reality worlds: prefrontal brain regions differentially orchestrate presence experience in adults and children. Frontiers in human neuroscience 2: 1-12.

Baumgartner, T., Valko, L., Esslen, M., & Jäncke, L. (2006). Neural correlate of spatial presence in an arousing and noninteractive virtual reality: an EEG and psychophysiology study. CyberPsychology & Behavior 9: 30-45.

Bayliss, J. D., & Ballard, D. H. (2000). A virtual reality testbed for brain-computer interface research. Rehabilitation Engineering, IEEE Transactions on, 8, 188-190.

Belliveau, J.W., Kennedy, D.N., McKinstry, R.C., Buchbinder, B.R., Weisskoff, R.M., Cohen, M.S., Vevea, J.M., Brady, T.J., & Rosen, B.R.

(1991). Functional Mapping of the Human Visual Cortex by Magnetic Resonance Imaging. Science, 254, 716-719. doi: 10.1126/science.1948051.

Bernstein, D. A., & Allen, G. J. (1969). Fear Survey Schedule (II): Normative data and factor analyses based upon a large college sample. Behaviour Research and Therapy, 7(4), 403-407.

Biocca, F., & Delaney, B. (1995). Immersive virtual reality technology. Communication in the age of virtual reality (F. Biocca, and M. Levy, Eds.), pp. 124. Lawrence Erlbaum Associates.

Born, R., & Bradley, D. (2005). Structure and function of visual area MT. Annu Rev Neurosci, 28, 157–89. doi:10.1146/annurev.neuro.26.041002.131052.

Botella, C., Baños, R. M., Perpiña, C., Villa, H., Alcañiz, M., & Rey, A. (1998). Virtual reality treatment of claustrophobia: A case report. Behaviour Research and Therapy, 36, 239–246.

Botella, C., Baños, R., Guillén, V., Perpiñá, C., Alcañiz, M., & Pons, A. (2000). Telepsychology: Public Speaking Fear Treatment on the Internet. CyberPsychology & Behavior, 3, 959-968.

Botella, C., Bretón-López, J., Quero, S., Baños, R., & García-Palacios, A. (2010). Treating Cockroach Phobia With Augmented Reality. Behavior Therapy, 41, 401–413.

Botella, C., García-Palacios, A., Villa, H., Baños, R., Quero, S., Alcañiz, M., & Riva, G. (2007). Virtual Reality Exposure in the Treatment of Panic Disorder and Agoraphobia: A Controlled Study. Clinical Psychology and Psychotherapy, 14, 164.

Botella, C., Quero, S., Baños, R.M., Perpiñá, C., García-Palacios, A., & Riva, G. (2006). Virtual Reality and Psychotherapy. Studies in Health Technology and Informatics, vol. 99, pp. 37-54, 2006.

Brown, T. A., DiNardo, P., & Barlow, D. H. (1994). Anxiety disorders interview schedule adult version (ADIS-IV): Client interview schedule. San Antonio, TX: Psychological Corporation.

Büchel, C., Josephs, O., Rees, G., Turner, R., Frith, C.D., & Friston, K.J. (1998). The functional anatomy of attention to visual motion: a functional MRI study. Brain, 121, 1281–1294.

Bush, J. (2008). Viability of virtual reality exposure therapy as a treatment alternative. Computers in Human Behavior, 24(3), 1032-1040.

Calhoun, V. D., Carvalho, K., Astur, R., & Pearlson, G. D. (2005). Using virtual reality to study alcohol intoxication effects on the neural correlates of simulated driving. Applied psychophysiology and biofeedback 30: 285– 306.

Campbell, A.T., Choudhury, T., Hu, S., Lu, H., Mukerjee, M.K., Rabbi, M., & Raizada, R.D.S. (2010). NeuroPhone: Brain-Mobile Phone Interface using a Wireless EEG Headset. MobiHeld '10 Proceedings of the second ACM SIGCOMM workshop on Networking, systems, and applications on mobile handhelds, Pages 3-8.

Canli, T., Zhao, Z., Desmond, J.E., Kang, E., Gross, J., & Gabrieli, J.D.E. (2001). An fMRI study of personality influences on brain reactivity to emotional stimuli. Behav Neurosci, 115, 33-42. doi: 10.1037/0735-7044.115.1.33.

Carlin, A. S., Hoffman, H. G., & Weghorst, S. (1997). Virtual reality and tactile augmentation in the treatment of spider phobia: A case report. Behaviour Research and Therapy, 35, 153–158.

Cavanna, A., & Trimble, M. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. Brain, 129, 564–583.

Chapman, D. L. (1997). The epidemiology of fears and phobias. In G. C. L. Davey (Ed.), Phobias. A handbook of theory, research and treatment. London: Wiley. pp. 415–434.

Chawla, D., Rees, G., & Friston, K.J. (1999). The physiological basis of attentional modulation in extrastriate visual areas. Nature Neurosci., 2, 671–676.

Choy, Y., Fyer, A. J., & Lipsitz, J. D. (2007). Treatment of specific phobia in adults. Clinical Psychology Review, 27, 266–286.

Christopoulos, G.I., Tobler, P.N., Bossaerts, P., Dolan, R.J., & Schultz, W. (2009). Neural Correlates of Value, Risk, and Risk Aversion Contributing to Decision Making under Risk. J Neurosci, 26, 6469–6472.

Craig, A.D. (2009). How do you feel now? The anterior insula and human awareness. Nat Rev Neurosci, 10, 59-70. doi:10.1038/nrn2555.

Craske, M. G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., & Baker, A. (2008). Optimizing inhibitory learning during exposure therapy. Behaviour Research and Therapy, 46, 5–27.

Cutshall, C., & Watson, D. (2004). The phobic stimuli response scales: A new self-report measure of fear. Behaviour Research and Therapy, 42, 1193–1201.

Delorme, A., & Makeig, E. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. Journal of Neuroscience Methods 134, 9-21.

Difede, J., & Hoffman, H. (2002). Virtual Reality Exposure Therapy for World Trade Center Post-Traumatic Stress Disorder: A Case Report. CyberPsychology & Behavior, 5, 529-535.

Dilger, S., Straube, T., Mentzel, H.J., Fitzek, C., Reichenbach, J., Hecht, H., Krieschel, S., Gutberlet, I., & Miltner, W.H.R. (2003). Brain activation to phobia-related pictures in spider phobic humans: an event-related functional magnetic resonance imaging study. Neurosci Lett, 348, 29-32. doi: 10.1016/S0304-3940(03)00647-5.

Dillon, C., Keogh, E., Freeman, J., & Davidoff, J. (2000). Aroused and immersed: the psychophysiology of presence. Paper presented at: 3rd International Workshop on Presence [Delft, The Netherlands].

DiNardo, P. A., Brown, T. A., & Barlow, D. H. (1994). Anxiety disorders interview schedule for DSM-IV: Lifetime version (ADIS-IV-L). New York: Graywind Publications.

Dodds, C.M., Morein-Zamir, S., & Robbind, T.W. (2011). Dissociating inhibition, attention, and response control in the frontoparietal

network using functional magnetic resonance imaging. Cereb Cortex, 21, 1155-1165. doi: 10.1093/cercor/bhq187.

Du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., Samson, Y., Zhang, S., & Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. Brain, 129, 3315-3328.

Duvinage, M., Castermans, T., Dutoit, T., Petieau, M., Hoellinger, T., De Saedeleer, C., Seetharaman, K., & Cheron, G. (2012). A p300-based quantitative comparison between the emotiv epoc headset and a medical eeg device. Proceedings of the IASTED International Conference Biomedical Engineering, Innsbruck, Austria: ACTA Press.

Emmelkamp, P. (2000). Technological innovations in Clinical Assessment and Psychotherapy. Psychotherapy and Psychosomatics, 74, 336-343.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. Nature, 392, 598-601. doi:10.1038/33402.

Etkin, A., & Wager, T.D. (2007). Fuctional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder and specific phobia. Am J Psychiatry, 164, 1476-1488.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods 39, 175-191.

Feeney, N., Hembree, E., & Zoellner, L. (2003). Myths regarding exposure therapy for PTSD. Cognitive and Behavioral Practice, 10, 85–90.

First, M. B., Spitzer, R. L, Gibbon, M., & Williams, J. B.W. (2007). Structured clinical interview for DSM-IV-TR axis I Disorders, Research Version, Patient edition. (SCID-I/P) New York: Biometrics Research, NewYork State Psychiatric Institute.

Fredrikson, M., Wik, G., Annas, P., Ericson, K., & Stone-Elander, S. (1995). Functional neuroanatomy of visually elicited simple phobic fear: additional data and theoretical analysis. Psychophysiology, 32, 43–48.

Fredrikson, M., Wik, G., Greitz, T., Eriksson, L., Stone-Elander, S., Ericson, K., & Sedvall, G. (1993). Regional cerebral blood flow during experimental phobic fear. Psychophysiology, 30, 126–130.

Freeman, J., Avons, S E., Pearson, D. E., & IJsselsteijn, W. A. (1999). Effects of sensory information and prior experience on direct subjective ratings of presence. Presence: Teleoperators & Virtual Environments 8: 1–13.

Frei, E., Gamma, A., Pascual-Marqui, R., Lehmann, D., Hell, D., & Vollenweider, F.X. (2001). Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA). Human Brain Mapping 14, 152-165.

Friston, K.J., Holmes, A.P., Poline, J-B., Grasby, P.J., Williams, S.C.R., Frackowiak, R.S.J., & Turner, R. (1995). Analysis of fMRI Time-Series Revisited. Neuroimage, 2, 45-53. doi:10.1006/nimg.1995.1007.

Frueh, B., Turner, S., & Beidel, D. (1995). Exposure therapy for combat related PTSD: a critical review. Clinical Psychology Review, 15, 799–817.

Furmark, T., Tillfors, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B., & Fredrikson, M. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. Archives of General Psychiatry, 59(5), 425.

Garbarini, F., & Adenzato, M. (2004). At the root of embodied cognition: cognitive science meets neurophysiology. Brain Cogn., 56, 100–106.

Garcia-Palacios, A., Hoffman, H., Carlin, A., Furness III, T.A., & Botella, C. (2002). Virtual reality in the treatment of spider phobia: a controlled study. Behaviour Research and Therapy, 40, 983-993.

Geake, J.G., & Hansen, P.C. (2005). Neural correlates of intelligence as revealed by fMRI of fluid analogies. NeuroImage, 26, 555-564. doi: 10.1016/j.neuroimage.2005.01.035.

Goldberg, I., Harel, M., & Malach, R. (2006). When the brain loses its self: prefrontal inactivation during sensorimotor processing. Neuron, 50, 329–339.

Grawe, K. (2007). Neuropsychotherapy: How the neurosciences inform effective psychotherapy. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers. xxiv 476 pp.

Grodd, W., Hülsmann, E., Lotze, M., Wildgruber, D., & Erb, M. (2001). Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum. Brain Mapp., 13: 55–73.

Grös, D. F., & Antony, M. M. (2006). The assessment and treatment of specific phobias: a review. Current psychiatry reports, 8(4), 298-303.

Haans, A., & IJsselsteijn, W.A. (2012). Embodiment and telepresence: Towards an comprehensive theory of presence. Interacting with Computers, 24, 211–218. doi:10.1016/j.intcom.2012.04.010.

Haldane, M., Cunningham, G., Androutsos, C., & Frangou, S. (2008). Structural brain correlates of response inhibition in Bipolar Disorder I. J Psychopharmacol, 22, 138-43. doi: 10.1177/0269881107082955.

Han, S., Jiang, Y., Humphreys, G., Zhou, T., & Cai, P. (2005). Distinct neural substrates for the perception of real and virtual visual worlds. NeuroImage 24, 928-935.

Heeter, C. (1992). Being there: The subjective experience of presence. Presence: Teleoperators & Virtual Environments, 1, 262–271.

Hendrix, C. & Barfield, W. (1996). The sense of presence within auditory virtual environments. Presence: Teleoperators & Virtual Environments, vol. 5, no. 3, pp. 290–301.

Hoffman, H. G., Richards, T. L., Coda, B., Bills, A. R., Blough, D., Richards, A. L., & Sharar, S. R. (2004). Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. Neuroreport 15: 1245.

Hoffman, H. G., Richards, T., Coda, B., Richards, A., & Sharar, S. R. (2003). The illusion of presence in immersive virtual reality during an fMRI brain scan. CyberPsychology & Behavior 6: 127–131.

Hood, H. K., & Antony, M. M. (2012). Evidence-based assessment and treatment of specific phobias in adults. In Intensive One-session Treatment of Specific Phobias (pp. 19-42). Springer New York.

IJsselsteijn, W. A., & Ridder, H. D. (1998). Measuring temporal variations in presence. Paper presented at Presence in Shared Virtual Environments Workshop [United Kingdom].

International Society for Presence Research (2000). The Concept of Presence: Explication Statement. Retrieved 10/28/2011 from http://ispr.info/

Jäncke, L., Cheetham, M., & Baumgartner, T. (2009). Virtual reality and the role of the prefrontal cortex in adults and children. Frontiers in Neuroscience, 3, 52-59. doi: 10.3389/neuro.01.006.20009.

Jang, D., Ku, J., Shin, M., Choi, Y., & Kim, S. (2000). Objective Validation of the Effectiveness of Virtual Reality Psychotherapy. CyberPSychology & Behavior, 3, 369-374.

Johanson, A., Gustafson, L., Passant, U., Risberg, J., Smith, G.,Warkentin, S., & Tucker, D. (1998). Brain function in spider phobia. Psychiatry Res.: Neuroimag. Sec., 84, 101–111.

Johanson, A., Risberg, J., Tucker, D.M., & Gustafson, L. (2006). Changes in frontal lobe activity with cognitive therapy for spider phobia. Appl Neuropsychol., 13, 34-41.

Johnson, P.B., Ferraina, S., Bianchi, L., & Caminiti, R. (1996). Cortical Networks for Visual Reaching: Physiological and Anatomical Organization of Frontal and Parietal Lobe Arm Regions. Cereb Cortex, 6, 102-119. doi: 10.1093/cercor/6.2.102.

Juan, M. C., & Calatrava, J. (2011). An Augmented Reality System for the Treatment of Phobia to Small Animals Viewed Via an Optical See-Through HMD: Comparison With a Similar System Viewed Via a Video See-Through HMD. International Journal of Human-Computer Interaction, 27(5), 436-449.

Kandel, E.R. (1996). Zelluläre Grundlanger von Lerner und Gedächtnis [Cellular mechanisms of learning and memory]. In E.R. Kandel, J.H. Schwartz & T.M. Jessell (Eds.), Neurowissenschaften. Heidelberg, germany: Spectrum Akademischer Verlag.

Karnath, H.O., Baier, B., & Nägele, T. (2005). Awareness of the functioning of one's own limbs mediated by the insular cortex? J. Neurosci., 25, 7134-8. doi: 10.1523/JNEUROSCI.1590-05.2005.

Kastner, S., O'Connor, D.H., Fukui, M.M., Fehd, H.M., Herwig, U., & Pinsk, M.A. (2004). Functional Imaging of the human lateral geniculate nucleus and pulvinar. J Neurophysiol, 91, 438-448.

Kawashima, R., Roland, P.E., & O'Sullivan, B.T. (1995). Functional anatomy of reaching and visuomotor learning: a positron emission tomography study. Cereb Cortex, 5, 111–122.

Kessler, R.C., Berglund, P.A., Demler, O., Jin, R., & Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry, 62, 593-602.

Khushaba, R.N., Kodagoda, S., Dissanayake, G., Greenacre, L., Burke, S., & Louviere, J. (2012). Neuroscientific Approach to Choice Modeling: Electroencephalogram (EEG) and User Preferences. Proceedings of the WCCI 2012 IEEE World Congress on Computational Intelligence, Brisbane (Australia).

Khushaba, R.N., Wise, C., Kodagoda, S., Louviere, J., Kahn, B.E., & Townsend, C. (2013). Consumer neuroscience: Assessing the brain response to marketing stimuli using electroencephalogram (EEG) and eye tracking. Expert Systems with Applications 40, 3803–3812.

Kim, T., & Biocca, F. (2006). Telepresence via Television: Two Dimensions of Telepresence May Have Different Connections to Memory and Persuasion. JCMC 3. doi: 10.1111/j.1083-6101.1997.tb00073.x.

Kimberg, D.Y., & Farah, M.J. (1993). A unified account of cognitive impairments following frontal lobe damage: the role of working memory in complex, organized behavior. J. Exp. Psychol. Gen., 122, 411-28.

Kjaer, T.W., Nowak, M., & Lou, H.C. (2002). Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. Neuroimage, 17, 1080–1086.

Klorman, R., Weerts, T. C., Hastings, J. E., Melamed, B. G., & Lang, P. J. (1974). Psychometric description of some specific-fear questionnaires. Behavior Therapy, 5, 401–409.

Kober, S.E., Kurzmann, J., & Neuper, C. (2012). Cortical correlate of spatial presence in 2D and 3D interactive virtual reality: An EEg study, International Journal of Psychophysiology 83, 365-374.

Kober, S.E., & Neuper, C. (2012). Using auditory event-related EEG potentials to assess presence in virtual reality, Int. J. Human-Computer Studies 70, 577-587.

Koechlin, E., Ody, C., & Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. Science, 302, 1181-1185. doi: 10.1126/science.1088545.

Kosslyn, S.M., Shin, L.M., Thompson, W.L., McNally, R.J., Rauch, S.L., Pitman, R.K., & Alpert, N.M. (1996). Neural effects of visualizing and perceiving aversive stimuli: A PET investigation. NeuroReport, 7, 1569–1576.

Krijn, M., Emmelkamp, P.M.G., Olafsson, R.P., & Biemond, R. (2004). Virtual reality exposure therapy of anxiety disorders: A review. Clinical Psychology Review, 24, 259-281.

Krolak-Salmon, P., Hénaff, M.A., Vighetto, A., Bertrand, O., & Mauguière, F. (2004). Early amygdala reaction to fear spreading in occipital, temporal, and frontal cortex: A depth electrode ERP study in human. Neuron, 42, 665-676.

Kwong, K.K., Belliveau, J.W., Chesler, D.A., Goldberg, I.E., Weisskoff, R.M., Poncelet, B.P., Kennedy, D.N., Hoppel, B.E., Cohen, M.S., Turner, R., Cheng, H.M., Brady, T.J., & Rosen, B.R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc. Natl. Acad. Sci., 89, 5675-5679.

Lang, P. J., Bradley, M. M., Fitzsimmons, J., Cuthbert, B. N., Scott, J. D., Moulder, B., & Nangia, V. (1998). Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35: 199-210.

Larson, C.L., Schaefer, H.S., Siegle, G.J., Jackson, C.A.B., Anderle, M.J., & Davidson, R.J. (2006). Fear Is Fast in Phobic Individuals: Amygdala Activation in Response to Fear-Relevant Stimuli. Biol Psychiatry, 60, 410–417.

Le Bihan, D., Turner, R., Zeffiro, T.A., Cuénod, C.A., Jezzard, P., & Bonnerot, V. (1993). Activation of human primary visual cortex during visual recall: A magnetic resonance imaging study. Proc. Natl. Sci. USA, 90, 11802-11805.

LeDoux, J.E. (1993). Emotional memory systems in the brain. Behav. Brain Res., 58, 69–79.

LeDoux, J.E. (2002). Synaptic self: How our brains become who we are. New York: Viking Penguin.

Lee, J. H., Lim, Y., Wiederhold, B. K., & Graham, S. J. (2005). A functional magnetic resonance imaging (fMRI) study of cue-induced smoking craving in virtual environments. Applied psychophysiology and biofeedback 30: 195–204.

Lessiter, J., Freeman, J., Keogh, E., & Davidoff, J. (2001). A cross-media presence questionnaire: the ITC-sense of presence inventory. Presence: Teleoperators and Virtual Environments 10: 282-298.

Lin, C. T., Chung, I. F., Ko, L. W., Chen, Y. C., Liang, S. F., & Duann, J. R. (2007). EEG-based assessment of driver cognitive responses in a dynamic virtual-reality driving environment. Biomedical Engineering, IEEE Transactions on, 54, 1349-1352.

Loomis, J.M. (1992). Distal attribution and presence. Presence, 1, 113-118.

Lou, H.C., Luber, B., Crupain, M., Keenan, J.P., Nowak, M., Kjaer, T.W., Sackeim, H.A., & Lisanby, S.H. (2004). Parietal cortex and representation of the mental Self. Proceedings of the National Academy of Sciences of the United States of America, 101, 6827–6832.

Magee, W.J., Eaton, W.W., Wittchen, H.U., McGonagle, K.A., & Kessler, R.C. (1996). Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry., 53, 159-68.

Meehan, M., Insko, B., Whitton, M., & Brooks, F.P. Jr. (2001). Physiological measures of presence in virtual environments. Paper presented at: 4th International Workshop on Presence [Philadelphia, Pennsylvania, USA].

Mellet, E., Laou, L., Petit, L., Zago, L., Mazoyer, B., & Tzourio-Mazoyer, N. (2010). Impact of the Virtual Reality on the neural representations of an environment. Hum Brain Mapp, 31, 1065-1075. doi: 10.1002/hbm.20917.

Mishkin, M., & Ungerleider, L.G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. Behav Brain Res., 6, 57-77. doi: 10.1016/0166-4328(82)90081-X.

Moore, K., Wiederhold, B., Wiederhold, M., & Riva, G. (2002). Panic and Agoraphobia in a Virtual World. Cyberpsychology & Behavior, 5, 197-202.

Mraz, R., Hong, J., Quintin, G., Staines, W. R., McIlroy, W. E., Zakzanis, K. K., & Graham, S. J. (2003). A platform for combining virtual reality experiments with functional magnetic resonance imaging. CyberPsychology & Behavior 6: 359-368.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatini, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., Kawamoto, M., Togao, O., & Kanba, S. (2005). Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: A functional magnetic resonance imaging study. Biol Psychiatry, 57, 901-910.

Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biological Psychiatry, 63, 1118–1126.

North, M.M., & North, S.M. (1996). Virtual Reality Psychotherapy. The Journal of Medicine and Virtual Reality, 1, 28-32.

North, M. M., North, S. M., & Coble, J. R. (1997a). Virtual reality therapy for fear of flying. American Journal of Psychiatry, 154, 130.

North, M.M., North, S.M., & Coble, J.R. (1997b). Virtual Reality Therapy: An Effective Treatment for Psychological Disorders. Virtual Reality in Neuro-Psycho-Physiology: Cognitive, Clinical and Methodological Issues in Assessment and Rehabilitation, 44, 59-70.

North, M.M., North, S.M., & Coble, J.R. (1997c). Virtual Environments Psychotherapy – A Case Study of Fear of Flying Disorder. Presence: Teleoperators and Virtual Environments, 6, 127-132.

North, M.M., North, S.M., & Coble, J.R. (1998). Virtual Reality Therapy: an Effective Treatment for Phobia. Studies in Health Technology and Informatics, vol. 58, pp. 112-119. Amsterdam, Netherlands: IOS Press.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. Journal of Cognitive Neuroscience 14: 1215-1229.

O'Craven, K.M., Rosen, B.R., Kwong, K.K., Treisman, A., & Savoy, R.L. (1997). Voluntary attention modulates fMRI activity in human MT-MST. Neuron, 18, 591–598.

Ogawa S., Lee T.M., Kay A.K. & Tank D.W., (1990). Brain Magnetic Resonance Imaging with Contrast Dependent on Blood Oxygenation Proc. Natl. Acad. Sci. (USA), 87, 9868-9872

Ogawa S., Tank D.W., R. Menon R.S., Ellermann J.M., Kim S. G., Merkle H. & Ugurbil K., (1992). Intrinsic Signal Changes Accompanying Sensory Stimulation: Functional Brain Mapping With Magnetic Resonance Imaging. Proc. Natl. Acad. Sci. (USA), 89, 5951-5955

Olatunji, B.O., Deacon, B.J., & Abramowitz, J.S. (2009). The cruelest cure? ethical issues in the implementation of exposure-based treatments. Cognitive and Behavioral Practice, 16, 172–180.

Oldfield, R.C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9, 97-113. doi:10.1016/0028-3932(71)90067-4.

Onitsuka, T., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Kasai, K., Toner, S.K., Frumin, M., Kikinis, R., Jolesz, F.A., & McCarley, R.W. (2004). Middle and Inferior Temporal Gyrus gray matter volume abnormalities in Chronic Schizophrenia: An MRI Study. Am J Psychiatry, 161, 1603-1611.

Orban, G.A. (2008). Higher Order Visual Processing in Macaque Extrastriate Cortex. Physiol Rev January 1, 88, 59-89.

Öst, L. G., & Hugdahl, K. (1981). Acquisition of phobias and anxiety response patterns in clinical patients. Behaviour Research and Therapy, 19(5), 439-447.

Owen, A.M., Downes, J.J., Sahakian, B.J., Polkey, C.E., & Robbins, T.W. (1990). Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia, 28, 1021-1034. doi: 10.1016/0028-3932(90)90137-D.

Papez, J.W. (1937). A proposed mechanism of emotion. Archives of neurology and psychiatry, 38, 725–43.

Paquette, V., Lévesque, J., Mensour, B., Leroux, J. M., Beaudoin, G., Bourgouin, P., & Beauregard, M. (2003). Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage 18: 401–409.

Parsons, T., & Rizzo, A. (2008). Affective outcomes of Virtual Reality Exposure Therapy for Anxiety and Specific Phobias: a Meta-Analysis. Journal of Behavior Therapy and Experimental Psychiatry, 39, 250-261.

Pascual-Marqui, R.D. (1999). Review of Methods for Solving the EEG Inverse Problem, International Journal of Bioelectromagnetism 1, 75-86.

Pascual-Marqui, R.D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M.C.G., Hell, D., & Koukkou, M. (1999). Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. Psychiatry Research-Neuroimaging 90, 169-179.

Pascual-Marqui, R.D., Michel, C.M., & Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. International Journal of Psychophysiology 18, 49-65.

Perani, D., Fazio, F., Borghese, N.A., Tettamanti, M., Ferrari, S., Decety, J., & Gilardi, M.C. (2001). Different brain correlates for watching real and virtual hand actions. NeuroImage, 14, 749-758. doi: 10.1006/nimg.2001.0872.

Perpiñá, C., Botella, C., Baños, R., Marco, H., Alcañiz, M., & Quero, S. (1999). Body Image and Virtual Reality in Eating Disorders: Is Exposure to Virtual Reality more Effective tan the Classical Body Image Treatment?. CyberPsychology & Behavior, 2, 149-155.

Pertaub, D., Slater, M., & Barker, C. (2002). An experiment on public speaking anxiety in response to three different types of virtual audience. Presence: Teleoperators & Virtual Environments, 11, 68-78.

Petersen, S.E., Robinson, D.L., & Keys, W. (1985). Pulvinar nuclei of the behaving rhesus monkey: visual responses and their modulation. J Neurophysiol, 54, 867–886.

Petrides, M. (2000). The role of the mid-dorsolateral prefrontal cortex in working memory. Exp Brain Res, 133, 44-54. doi: 10.1007/s002210000399.

Pine, D.S., Grun, J., Maguire, E. A., Burgess, N., Zarahn, E., Koda, V., Fyer, A., Szeszko, P. R., & Bilder, R. M. (2002). Neurodevelopmental aspects of spatial navigation: a virtual reality fMRI study. Neuroimage 15: 396– 406.

Porro, C.A., Cettolo, V., Francescato, M.P., & Baraldi, P. (2003). Functional activity mapping of the mesial hemispheric wall during anticipation of pain. NeuroImage, 19, 1738–1747.

Poza, J.J., & Marí, J.F. (2006). Total dream loss secondary to left temporo-occipital brain injury. Neurologia, 21, 152-154.

Prochaska, J.O., & Norcross, J.C. (1999). Systems of Psychotherapy: A Transtheoretical Analysis fourth ed. Brooks/Cole, Pacific Grove, CA.

Purcell, R., Maruff, P., Kyrios, M., & Pantelis, C. (1998). Cognitive deficits in obsessive-compulsive disorder in tests of frontal-striatal function. Biol Psychiatry, 43, 348–357.

Radua, J., Phillips, M.L., Russell, T., Lawrence, N., Marshall, N., Kalidindi, S., El-Hage, W., McDonald, C., et al. (2010). Neural response to specific components of fearful faces in healthy and schizophrenic adults. NeuroImage, 49, 939–946.

Rey, B., Alcañiz, M., Tembl, J., & Parkhutik, V. (2010a). Brain activity and presence: a preliminary study in different immersive conditions using transcranial Doppler monitoring. Virtual Reality 14: 55-65.

Rey, B., Montesa, J., Alcañiz, M., Baños, R., & Botella, C. (2005). A Preliminary Study on the Use of an Adaptive Display for the Treatment of Emotional Disorders. Psychnology Journal, 3, 101-112.

Rey, B., Naranjo, V., Parkhutik, V., Tembl, J., & Alcañiz, M. (2010b). A new visually evoked cerebral blood flow response analysis using a low-frequency estimation. Ultrasound in Medicine & Biology 36: 383-391.

Rice University. (2011). Temporal Lobe. Langbrain. Retrieved from http://www.ruf.rice.edu/~lngbrain/cglidden/temporal.html

Richard, D.C.S., & Gloster, A.T. (2007). Exposure therapy has a public relations problem: a dearth of litigation amid a wealth of concern. In: Richard, D.C.S., Lauterbach, D. (Eds.), Comprehensive Handbook of the Exposure Therapies. New York: Academic Press.

Riva, G. (2010). Using Virtual Immersion Therapeutically. Use of technology in Mental Health. Applications, ethics and practice. Springfield, IL: CC. Thomas Publisher.

Riva, G., Bacchetta, M., Baruffi, M., Rinaldi, S., & Molinari, E. (1998). Experiential Cognitive Therapy: A VR Based Approach for the Assessment and Treatment of Eating Disorders, Studies in Health Technology and Informatics, 58, 120.

Riva, G., Bacchetta, M., Cesa, G., Conti, S., Castelnuovo, G., Mantovani, F., & Molinari, E. (2006). Is Severe Obesity a Form of

Addiction? Rationale, Climinal Approach and Controllled Clinical Trial. CyberPsychology & Behavior, 9, 457-479.

Riva, G., Davide, F., & IJsselsteijn, W.A. (2003). Being There: Concepts, effects and measurement of user presence in synthetic environments. Ios Press, Amsterdam, The Netherlands.

Riva, G., Waterworth, J.A., Waterworth, E.L., & Mantovani, F. (2011). From intention to action: The role of presence. New Ideas in Psychology, 29, 24-37. doi:10.1016/j.newideapsych.2009.11.002.

Rizzo, A., Paier, J., Graap, K., Manson, B., McNerney, P., Wiederhold, B., Wiederhold, M., & Spira, J. (2006). A Virtual Reality Exposure Therapy Application for Iraq War Military Personnel with Post Traumatic Stress Disorder: From Training to Toy to Treatment. NATO Security Through Science Series E. Human and Societal Dynamics, 6, 235.

Rodríguez, A., Rey, B., & Alcañiz, M. (2013a). Evaluating Virtual Reality Mood Induction Procedures with Portable EEG Devices. Proceedings of the Cybertherapy 2013, 18th Annual CyberPsychology and CyberTherapy Conference, Brussels (Belgium).

Rodríguez, A., Rey, B., & Alcañiz, M. (2013b). Validation of a Low-Cost EEG Device for Mood Induction Studies. Proceedings of the Cybertherapy 2013, 18th Annual CyberPsychology and CyberTherapy Conference, Brussels (Belgium).

Rosen, B.R., Belliveau, J.W., Buchbinder, B.R., McKinstry, R.C., Porkka, L.M., Kennedy, D.N., Neuder, M.S., Fisel, C.R., Aronen, H.J., Kwong, K.K., Weisskoff, R.M., Cohen, M.S., & Brady, T.J. (1991). Contrast agents and cerebral hemodynamics. Magnetic resonance in medicine, 19, 285-292.

Rothbaum, B. O., Hodges, L., Kooper, R., Opdyke, D., Williford, J. S., & North, M. (1995a). Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. American Journal of Psychiatry, 152, 626–628.

Rothbaum, B. O., Hodges, L., Kooper, R., Opdyke, D., Williford, J. S., & North, M. (1995b). Virtual Reality Graded Exposure in the Treatment of Acrophobia: A Case Report. Behavior Therapy, 26, 547-554.

Rothbaum, B., Hodges, L., Ready, D., Graap, K., & Alarcon, R. (2001). Virtual Reality Exposure Therapy for Vietnam Veterans with Posttraumatic Stress Disorder. Journal of Clinical Psychiatry.

Rothbaum, B., Hodges, L., Watson, B., Kessler, G., & Opdyke, D. (1996). Virtual Reality Exposure Therapy in the Treatment of Fear of Flying: A Case Report. Behaviour Research and Therapy, 34, 477-481.

Rowe, M. K., & Craske, M. G. (1998). Effects of varied-stimulus exposure training on fear reduction and return of fear. Behaviour Research and Therapy, 36, 719–734.

Sadowski, W., & Stanney, K. (2002). Presence in virtual environments. Handbook of virtual environments: Design, implementation, and applications (K. Stanney, Ed.), pp. 791–806. New Jersey: Lawrence Erlbaum Associates.

Sanchez-Vives, M.V., & Slater, M. (2005). From presence to consciousness through virtual reality. Nat Rev Neurosci, 6, 332-339. doi:10.1038/nrn1651.

Sanjuan, J., Lull, J. J., Aguilar, E. J., Martí-Bonmatí, L., Moratal, D., Gonzalez, J. C., Robles, M., & Keshavan, M. S. (2007). Emotional words induce enhanced brain activity in schizophrenic patients with auditory hallucinations. Psychiatry Research: Neuroimaging 154: 21–29.

Sanjuan, J., Lull, J. J., Martí-Bonmatí, L., Aguilar, E. J., Moratal, D., Gonzalez, J. C., & Robles, M. (2005). Emotional auditory paradigm in neuroimaging: a base for the study of psychosis. Actas Españolas de Psiquiatría 33: 383-389.

Scharmüller, W., Leutgeb, V., Schäfer, A., Köchel, A., & Schienle, A. (2011). Source localization of late electrocortical positivity during symptom provocation in spider phobia: An sLORETA study. Brain Res, 1397, 10-18.

Scheibe, C., Wartenburger, I., Wüstenberg, T., Kathmann, N., Villringer, A., & Heekeren, H.R. (2006). Neural Correlates of the Interaction Between Transient and Sustained Processes: A Mixed Blocked/Event-Related fMRI Study. Hum Brain Mapp, 27, 545-551. doi: 10.1002/hbm.20199.

Schienle, A., Schäfer, A., Hermann, A., Rohrmann, S., & Vailt, D. (2007). Symptom provocation and reduction in patients suffering from spider phobia. Eur Arch Psychiatry Clin Neurosci, 257, 486-493.

Schienle, A., Schäfer, A., Walter, B., Stark, R., & Vaitl, D. (2005). Brain activation of spider phobics towards disorder-relevant, generally disgust-and fear-inducing pictures. Neuroscience letters 388:1–6.

Schubert, T., Friedmann, F., & Regenbrecht, H. (2001). The experience of presence: factor analytic insights. Presence: Teleoperators and Virtual Environments 10: 266–281.

Schuemie, M. J., & van der Mast, C. A. P. G. (2001). VR Testbed configuration for phobia treatment research. In Proceedings of the Euromedia 2001 Conference, April (pp. 18-20).

Sharp, H., Rogers, Y., & Preece, J. (2007). Interaction design: Beyond human-computer interaction, 2nd ed. New York: John Wiley & Sons

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavas, J., Weiller, E., et al. (1998). The mini-international neuropsychiatric interview (M. I. N. I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry, 59, 22–33.

Sheridan, T. B. (1992). Musings on telepresence and virtual presence. Presence: Teleoperators & Virtual Environments 1: 120-126.

Sherman, S. (2006). Thalamus. Scholarpedia 1, 1583.

Sjölie, D. (2012). Presence and general principles of brain function. Interacting with Computers. doi:10.1016/j.intcom.2012.04.004

Sjölie, D., Bodin, K., Elgh, E., Eriksson, J., Janlert, L.-E., & Nyberg, L. (2010). Effects of interactivity and 3D-motion on mental rotation brain activity in an immersive virtual environment. Proceedings of the 28th international conference on Human factors in computing systems (pp. 869-878). Atlanta, Georgia, USA: ACM. doi:10.1145/1753326.1753454.

Smith, S.M. (2004). Overview of fMRI analysis. Br J Radiol, 77, 167-175. doi: 10.1259/bjr/33553595.

Slater, M., Pertaub, D., & Steed, A. (1999). Public Speaking in Virtual Reality: Facing an Audience of Avatars. Computer Graphics and Applications, EEE, 19, 6-9.

Slater, M. & Steed, A. (2000). A virtual presence counter. Presence: Teleoperators & Virtual Environments 9: 413–434.

Slater, M., Usoh, M., & Chrysanthou, Y. (1995). The influence of dynamic shadows on presence in immersive virtual environments. Presented at Selected papers of the Eurographics workshops on Virtual environments [Barcelona, Spain], 8–21, Springer-Verlag.

Slater, M., & Wilbur, M. (1997). A framework for immersive virtual Environments (FIVE)- speculations on the role of presence in virtual environments. Presence: Teleoperators & Virtual Environments 6: 603–616.

Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., He, Y., Yan, C.G., & Zang, Y.F. (2011). REST: A Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing. PLoS ONE, 6(9).

Straube, T., Glauer, M., Dilger, S., Mentzel, H.J., & Miltner, W.H.R. (2006). Effects of cognitive-behavioral therapy on brain activation in specific phobia. NeuroImage, 29, 125-135.

Straube, T., Kolassa, I. T., Glauer, M., Mentzel, H. J., & Miltner, W. H. R. (2004). Effect of task conditions on brain responses to threatening faces in social phobics: an event-related functional magnetic resonance imaging study. Biological Psychiatry 56: 921–930.

Straube, T., Mentzel, H. J., & Miltner, W. H. R. (2007). Waiting for spiders: brain activation during anticipatory anxiety in spider phobics. Neuroimage 37: 1427–1436.

Szymanski, J., & O'Donohue, W. (1995). Fear of spiders questionnaire. Journal of Behavior Therapy and Experimental Psychiatry, 26, 31–34.

Tarr, M., & Warren, W. (2002). Virtual reality in behavioral neuroscience and beyond. Nature Neuroscience 5: 1089–1092.

Usoh, M., Catena, E., Arman, S., & Slater, M. (2000). Using presence questionnaires in reality. Presence: Teleoperators and Virtual Environments 9: 497–503.

Vanni, S., Tanskanen, T., Seppä, M., Uutela, K., & Hari, R. (2001). Coinciding early activation of the human primary visual cortex and anteromedial cuneus. Proc Natl Acad Sci USA, 98, 2776-2780. doi: 10.1073/pnas.041600898.

Vincelli, F., & Riva, G. (2002). Virtual reality: A new tool for panic disorder therapy [Electronic version]. Expert Review of Neurotherapeutics,2, 89–95.

Wald, J., & Taylor, S. (2000). Efficacy of virtual reality exposure therapy to treat driving phobia: A case report. Journal of Behaviour Therapy and Experimental Psychiatry, 31, 249–257.

Waterworth, J. A., Waterworth, E. L., & Westling, J. (2002). Presence as performance: The mystique of digital participation. Paper presented at the Presence 2002: Fifth Annual International Workshop, Porto, Portugal.

Watts, F. N., & Sharrock, R. (1984). Questionnaire dimensions of spider phobia. Behaviour Research and Therapy, 22, 575–580.

Welch, R., Blackmon, T., Liu, A., Mellers, B., & Stark, L. (1996). The effects of pictorial realism, delay of visual feedback, and observer interactivity on the subjective sense of presence. Presence-teleop virt, 5, 263-273.

Wendt, J., Lotze, M., Weike, A. I., Hosten, N., & Hamm, A. O. (2008). Brain activation and defensive response mobilization during sustained exposure to phobia-related and other affective pictures in spider phobia. Psychophysiology, 45, 205–215.

Willshaw, D. (1999). The cerebellum as a neuronal machine. Self-Learning Robots III Brainstyle Robotics: The Cerebellum Beyond Function Approximation.

Witmer, B.G., & Singer, M. J. (1998). Measuring presence in virtual environments: a presence questionnaire. Presence: Teleoperators and Virtual Environments 7: 225-240.

Wolf, U., Rapoport, M.J., & Schweizer, T.A. (2009). Evaluating the affective component of the cerebellar cognitive affective syndrome. J. Neuropsychiatry Clin. Neurosci., 21, 245-53. doi: 10.1176/appi.neuropsych.21.3.245.

Wolitzky-Taylor, K. B., Horowitz, J. D., Powers, M. B., & Telch, M. J. (2008). Psychological approaches in the treatment of specific phobias: A meta-analysis. Clinical Psychology Review, 28, 1021–1037.

Wolpe, J., & Lazarus, A. A. (1966). Behavior therapy techniques: A guide to the treatment of neuroses. NewYork: Pergamon Press.

You, S. H., Jang, S. H., Kim, Y. H., Hallett, M., Ahn, S. H., Kwon, Y. H., Kim, J. H., & Lee, M. Y. (2005). Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. Stroke 36: 1166.

Zielinsli, C.M., Taylor, M.A., & Juzwin, K.R. (1991). Neuropsychological deficits in obsessive-compulsive disorder. Neuropsychiatry Neuropsychol Behav Neurol, 4, 110–126.