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RESONANCIA MAGNÉTICA FUNCIONAL CON PARADIGMA AUDITIVO EMOCIONAL EN PACIENTES CON UN PRIMER EPISODIO PSICÓTICO.

FUNCTIONAL MAGNETIC RESONANCE IMAGING USING AN AUDITORY EMOTIONAL PARADIGM IN FIRST-EPISODE PSYCHOSIS PATIENTS.

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“It is not the strongest of the species that survives,
not the most intelligent that survives.
It is the one that is the most adaptable to change.”
— Charles Darwin

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La presente Tesis es un esfuerzo en el cual, directa o indirectamente, han participado varias personas leyendo, opinando, corrigiendo, teniendo paciencia, dando ánimo y acompañándome en los momentos difíciles y en los momentos de felicidad.

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CHAPTER I: CONCEPTUAL FRAMEWORK AND META-ANALYSIS OF THE LITERATURE

1. INTRODUCTION

Psychosis, is one of the most important health issues within mental health. The disorder consists of a loss of contact with reality due to delusions or altered perception (Owen *et al.*, 2016). In particular, psychotic disorders are among the most severe disorders in terms of human suffering and social cost (Gustavsson *et al.*, 2011). Therefore, psychosis is a major social burden due to the tendency to chronicity, the impact on physical health, the reduction of life expectancy in a mean of 14.5 years (Hjorthøj *et al.*, 2017). Also, the risk of all-cause mortality associated with these disorders is greater than two-fold the general population. Thus, it is crucial to understand the mechanisms involved over the course of the illness (Fusar-Poli *et al.*, 2017). The first symptoms appear, generally, during adolescence, and the evolution is chronic or recurrent in half of the cases (Andreasen *et al.*, 1996). This interpretation has been reinforced by neuroimaging studies that have shown progressive changes in brain structure (Andreasen *et al.*, 2011). But, there is another reason to consider the clinical decline that is often observed in patients with psychosis as inevitable and could be a reflection not only of nonadherence and resulting relapses but also of the consequences of other critical elements of health such as poverty, homelessness, unemployment, and a lack of social support, as well as other comorbidities, that all too often confuse the course of the mental illness (van Os *et al.*, 1997).

After all, diagnosis and treatment are still clinico-phenomenological, despite the great advances that have ocurred, however, the clinical heterogeneity and the variability of research designs, prevent from obtaining a comprehensive vision of the evidence generated (Keshavan *et al.*, 2011).

Further, the clinical complexity of psychosis makes the road long and difficult due to a lack of specific diagnostic markers. Thus, although many advances have been made in the last years, old questions linger and new questions arise every day.

1.1 Risk factors of psychotic disorder.

A recent study observed considerable heterogeneity in risk for psychotic disorders, not only by person, but notably, by place, suggesting that the social environment may shape incidence patterns of Frist-Episode Psychosis (FEP). Along these lines, the study confirmed including higher rates in younger men, racial/ethnic minorities, and areas characterized by a lower percentage of owner-occupied houses, implicating socioeconomic factors in the prevalence of psychotic disorders (Jongsma *et al.*, 2018).

In a prospective study of an average of 34 new cases every 100,000 person-years (Kirkbride *et al.*, 2017). The evidence of a genetic predisposition is corroborated by the existence of families with multiple affected individuals (Lichtenstein *et al.*, 2009). Still, studies suggest that genetic and environmental risk factors should be considered together since both are important in the etiology of psychosis and do not seem to work in isolation (van Os *et al.*, 2008; van Os, 2014).

As such, a wide variety of biological and psychosocial factors --such as minority group position, urban environment, childhood trauma, and drug use-- have been associated with an increased risk of developing psychosis disorders (van Os *et al.*, 2010).

1.2 Early interventions following psychotic symptoms.

Detection and early intervention programs have been launched in several countries of the world, with, (McGorry *et al.*, 1996) Australia having led the way, followed by the United States, Europe, parts of Asian and some Latin American countries.

FEP is described by the initial appearance of psychotic symptoms in an individual´s life. The disorder is characterized by an array of so-called “positive symptoms” (e.g. delusions and hallucinations), “negative symptoms” (e.g. flat affect or social withdrawal), and “cognitive symptoms” (e.g. impaired cognitive memory) (Kahn *et al.*, 2015). The symptoms can be highly disturbing and unfamiliar, leaving the person confused and distressed. Schizophrenia is considered the most serious expression of a psychotic disorder and, it would include other diagnoses such as schizophreniform disorder, schizoaffective disorder, brief psychotic episode, psychosis not otherwise specified, and affective psychoses (bipolar disorder and major depression with psychotic symptoms) as well as psychosis associated with substance use or medical conditions (Peralta *et al.*, 2003).

The number and type of categories make psychotic disorders heterogeneous, complex, and multifactorial. In this vein, the psychotic spectrum differs in severity, frequency, chronicity, and prognosis, which changes depending on etiological and risk factors. In this context, a multinational study as part of the European network of national schizophrenia networks studying Gene–Environment Interactions (EU-GEI) found that psychopathology holds across diagnostic categories of non-affective and affective psychosis and demographic (Quattrone *et al.*, 2018).

Typically, signs appear either in late adolescence or at the beginning of adulthood, causing important alterations in all areas of life such as education, employment and social function (Jongsma *et al.*, 2018). The disorders of the psychotic spectrum usually present a chronic and episodic course that approximately affects between 5% and 8% of the general population (van Os *et al.*, 2008).

Although pharmacological and psychosocial treatments have significantly helped to alleviate symptoms and improve quality of life, a satisfactory recovery at a psychological and functional level is hardly ever achieved. However, in recent decades, increasing optimism around the possibility of improving the prognosis of psychosis and thus changing the traditional course of the disease or, at least, helping to improve the clinical course of the disorder by reducing its impact to long term.

This optimism comes from the psychiatric supports in emphasizing the differentiation, affinity diagnosis and treatment at the early stages of the psychotic disorders, differentiating the early clinical phenomena from those that characterize the progression to chronicity in order to provide adequate interventions for each phase of the disorder and, therefore, more effective treatments and fewer days than those provided in later phases (McGorry *et al.*, 2010).

As such, early intervention in first-episode psychotic patients is a worthy field of study because insight in this area allows mental health care professionals to minimize the impact of multifaceted confusion factors such as the duration of illness and long term antipsychotic treatment (Kapur *et al.*, 2012).

1.3 Diagnostic criteria for psychotic disorders.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) of American Psychiatric Association (American Psychiatric Association., 2013) and the International Classification of Diseases (World Health Organization., 2018) define psychosis narrowly by demanding the manifestation of hallucinations (without insight into their pathologic nature), delusions, or both hallucinations without insight and delusions.

In both of these existing diagnostic classification systems, impaired reality testing remains central conceptually to psychosis. Also, delusions such as fixed false beliefs, by definition are evidence of impaired reality testing: delusional beliefs are ones maintained persistently even in the face of evidence contradicting them unquestionably.

Similarly, hallucinations such as perceptions occurring in the absence of corresponding external stimuli are evidence of impaired reality when the individual experiencing them is unable to recognize the hallucinatory nature of such experiences.

Both the current DSM-V (American Psychiatric Association., 2013) and the ICD-11 (World Health Organization., 2018) classification systems admit that “formal thought disorder” such as disorganized thinking, including illogicality, tangentiality, perseveration, neologism, thought blocking, derailment, or some combination of these disturbances of thought is one of several commonly co-occurring features of psychotic disorders.

1.4 The phenomena of psychosis related to FEP.

Many attempts have been made to carry forward, refine or break up the symptoms. In this sense, although the first typology based on the differentiation of "positive" and "negative" symptoms was formulated by Crow (Crow, 1980), it was Jackson (Jackson, 1875) who began to use the "positive-negative" distinction. He believed that those identified as positive symptoms, hallucinations and delusions, were phenomena of liberation due to lack of control over the functions; while the negative symptoms, such as apathy or dull affect, reflected lack of function.

In this respect, these symptoms (delusions and hallucinations) are evidently defined common features of psychosis disorders. The interest in the distinction of symptoms made it necessary to create systems and instruments for evaluation and quantification. They are captured by informal and structured clinical assessments and are reasonably susceptible to treatment. The Positive and Negative Syndrome Scale (PANSS) is a widely used instrument for measuring symptomatology in patients with schizophrenia. It refers to three dimensions: Positive, negative, and general psychopathology.

The PANSS, was developed by Kay et al (Kay *et al.*, 1987) and adapted to Spanish by Peralta and Cuesta (Peralta *et al.*, 1994). This scale is one of the most widely used instruments to assess symptomatology in patients with schizophrenia. It is a heteroapplicated scale that is completed from a semi-structured interview of about 45 minutes long.

The PANSS is comprises 30 items grouped into three factors: Positive syndrome (composed of 7 items), negative syndrome (also composed of 7 items) and general psychopathology (composed of 16 items) (see in Annex I: Data collection booklet at First-Episode Psychosis Unit of the Hospital Universitario Clínico of Valencia).

1.5 Symptoms change over the course of disorder.

First episode psychosis refers to the first time someone experiences psychotic symptoms or a psychotic episode. Some of the more common types of psychotic disorders include schizophrenia, which is characterized by a sequential trajectory that implies different phases the first is called premorbid phase, subjects who develop schizophrenia exhibit previously a series of behavioral problems, emotional, and cognitive, accompanied by alterations in function academic and social. These abnormalities include delayed motor development, dysfunction attentional, deficits in language, low academic achievement, social isolation, and emotional indifference (Schenkel *et al.*, 2004).

A low premorbid function is associated with an early age of onset of psychosis and greater severity of cognitive symptoms (MacBeth *et al.*, 2007; Jeppesen *et al.*, 2008). However, the premorbid symptoms, are not present in all patients nor are they specific to those people who subsequently developed schizophrenia.

The subsequent period of time, a phase premature and prior to the onset of psychosis, has been described as the prodromal phase, characterized by attenuated positive symptoms as well as other clinical signs including cognitive disturbances, negative symptoms, symptoms of the state of mood and functional

deterioration (Riecher-Rössler *et al.*, 1998).

The prodrome can last from months to years, with an average of about five years (Häfner *et al.*, 1999; Klosterkötter, 2008).

The first psychotic episode announces the formal onset of psychosis, the initial period of the illness usually marked by exacerbations and remissions, with psychotic symptoms that are resolved to a greater or lesser extent between these episodes and that can vary between patients and the length of the disease course (Andreasen *et al.*, 2005). Finally, a stable phase occurs when the cognitive, positive and negative symptoms are increasingly dominant (Figure 1).

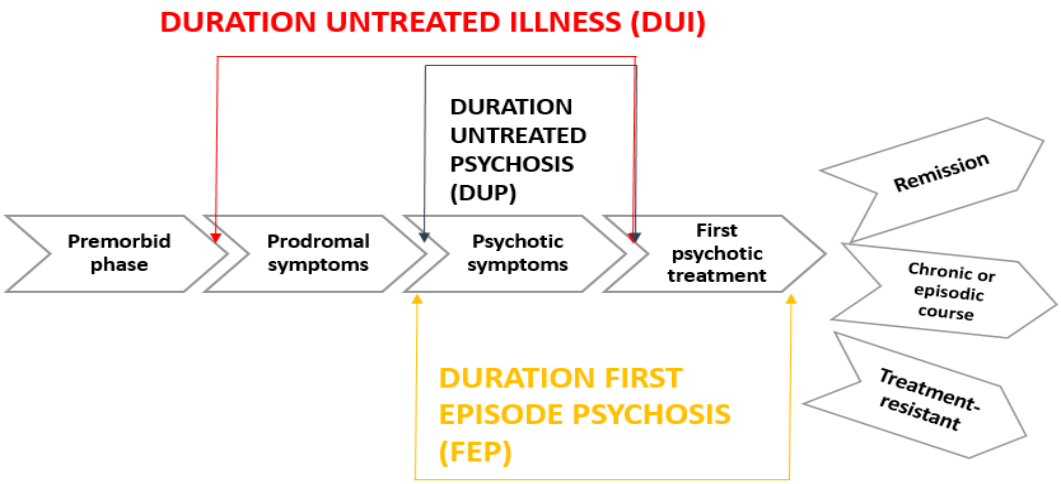

Figure 1: Stages throughout of Psychotic disorder

The interventions in the premorbid phase should be aimed at early recognition of risk factors and prevention. In the prodromal symptoms, prevention may be treating the sub-thresholds symptoms, which would reduce the risk of developing psychosis and in the first psychotic symptoms, the objective would be identification and early medical intervention, which could prevent the progression of the disease and improves time recovery rates (Lally *et al.*, 2017).

However, while most individuals with acute psychotic symptoms respond to antipsychotics (Leucht *et al.*, 2012) in some patients the course of the illness is characterized by a relapse-remitting pattern (Kahn *et al.*, 2015).

Thus, advances in antipsychotics drugs, genetics and neuroimaging have emergenced as new technologies to examine the ability of biomarkers to predict risk of psychotic relapse.

1.6 Biological markers in FEP.

A biomarker is a characteristic that can be measured objectively and that is related to a specific biological process, a pathological abnormality, or a response to treatment (Biomarkers Definitions Working Group., 2001). These characteristics should help to define an early diagnosis, the assessment of illness, as well as progression and the follow-up of therapeutic success.

Currently, many biomarkers have been proposed, but few have been useful to the clinical practice due to the clinical heterogeneity of the samples and the variability in the research designs.

One of the principal instruments used in biomarkers research for FEP is Magnetic Resonance Imaging (MRI) (Northoff *et al.*, 2011). Many studies have used volumetric changes in the brain during psychosis over time (Wright *et al.*, 2000).

Nevertheless, structural MRI changes are not specific and cannot be used as predictors in individual cases, so more sensitive instruments are needed (Shenton *et al.*, 2001; Brugger *et al.*, 2017; Cavelti *et al.*, 2018).

On one hand, there are several neuroimaging studies that have assessed as possible biomarkers examining brain abnormalities using different methodologies, such as diffusion tension imaging (DTI) focusing on the integrity of white matter tracks (Crossley *et al.*, 2017) and electroencephalography (EEG) (Murphy *et al.*, 2019). However, these methodologies have been applied with the promise of imminent clinical utility. Despite the continuing efforts, no diagnostic or prognostic biomarker for clinical use is available.

Another imaging method developed in order to demonstrate changes in brain metabolism is functional MRI (fMRI), which could provide a new important understanding about what happens in the brain during processing a different stimuli (Palaniyappan *et al.*, 2013; Roiser *et al.*, 2013; Pankow *et al.*, 2015; Smieskova *et al.*, 2015).

1.7 Functional Magnetic Resonance Imaging (fMRI).

Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging technique that employs MRI to image study hemodynamic changes in brain tissue that are caused by changes in neural metabolism.

Alterations of neural activity may be caused by asking the subject to perform a task designed to target a specific task process, or can occur spontaneously while the subject is resting in the absence of conscious mentation (i.e., in the “resting state”).

Both types of studies --task-based and resting state— are vital tools for studying cognition in healthy as well as diseased brains, and more than 200.000 studies have been listed in pubmed under “fMRI AND Brain”.

https://www.ncbi.nlm.nih.gov/pubmed/?term=fMRI%3B+Brain.

Since the first fMRI brain scans of the 1990s, scientists have achieved great progress not only in technical procedures employed to acquire brain imaging data but also in data processing methods that subsequently reveal an inspiring understanding of the brain drawn from various data perspectives.

In this sense, fMRI has become the dominant technique in neuroimaging due to its noninvasiveness, lack of radiation exposure, a relatively good spatial and temporal resolution, and relative ease to acquire (Zhan *et al.*, 2015).

Additional neuroimaging techniques including fMRI have been used in psychiatric disorders such as Computed Tomography (CT), Spectroscopy MRI and Tomography by emission of positron (PET). These techniques enable brain probes

at unprecedentedly high temporal or spatial resolution without the use of invasive techniques.

In contrast, fMRI make it possible to detect small local magnetic changes that occur as a consequence of the different susceptibility magnetic in the blood with oxygen (oxyhemoglobin) and without oxygen (deoxyhemoglobin) the mechanism term is well known as Blood Oxygenation Level Dependent (BOLD) contrast, which was first demonstrated in animals (Ogawa *et al.*, 1990) and then in humans (Ogawa *et al.*, 1993) and is this contrast that is applied in all conventional fMRI investigations.

BOLD contrast results from the change in magnetic field adjacent the red blood cells depending on the oxygen state of the hemoglobin. In fMRI studies when task activation is used, the aim is to induce different neural states in the brain using the visual, auditory or other stimulus during the scan, and activation maps are acquired by comparing the signals recorded. Furthermore, the variations of oxygenation are very subtle, which means that fMRI results are more accurate in high magnetic equipment field (eg, 3 tesla instead of 1.5 tesla), which is mostly sensitive to BOLD contrast in the draining veins (Krüger *et al.*, 2001).

There are several major MRI methods widely used in psychiatric neuroimaging shown below (Figure 2). Some methods focus on regional changes, whereas others take a systematic approach and emphasize on the whole brain network.

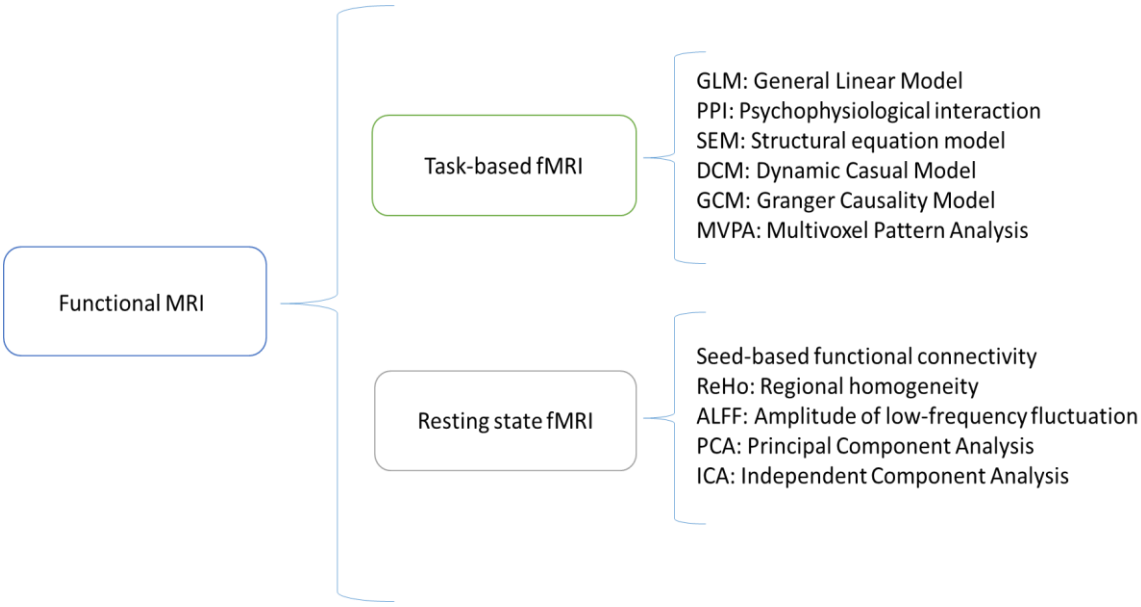

Figure 2:Summary of meanstream functional MRI methods

We will not examine all these methods because some of them are beyond the scope of this study. Therefore, we will focus particularly on General Lineal Model (GLM) (Friston *et al.*, 1995), which is the dominant method used in task-based fMRI in psychiatric research and the most common statistical method for assessing task brain activity relationships in neuroimaging (Worsley *et al.*, 1995).

It is a linear statistical analysis method that subsumes many basic analysis techniques, including t-tests, ANOVA, and multiple regression. The GLM can assist with numerous tests including whether the brain responds to a single type of event, comparison of different types of events, and correlations between brain activity and behavioral performance or other psychological variables. Studies on psychiatric disorders have used GLM method to compare brain activities induced by certain experimental manipulations in the patient and control group.

An fMRI dataset, can be seen as a set of cuboid elements known as “voxels” which

are the basic unit of a three-dimensional digital representation of an image or object. Each voxel in the resulting scan produces a time series that is subsequently analyzed in accordance to the task design (Glover, 2011). The first step in fMRI data analysis is to apply a series of “pre-processing” algorithms with the aim of correcting for several potential artifacts introduced at data acquisition. Each transformation can be applied as required depending on the specific experimental design or acquisition protocol.

Prior to statistical analysis, fMRI data undergoes a series of preprocessing steps which aim to (i) minimize the influence of data acquisition and physiological artifacts, (ii) check statistical assumptions and transform the data to meet these assumptions, and (iii) standardize the location of brain regions across different subjects to achieve validity and sensitivity in group analysis.

The major pre-processing steps performed on fMRI data (Figure 3) include reconstruction, slice-timing correction, motion correction, co-registration of structural and functional images, normalization to standard space, and spatial smoothing.

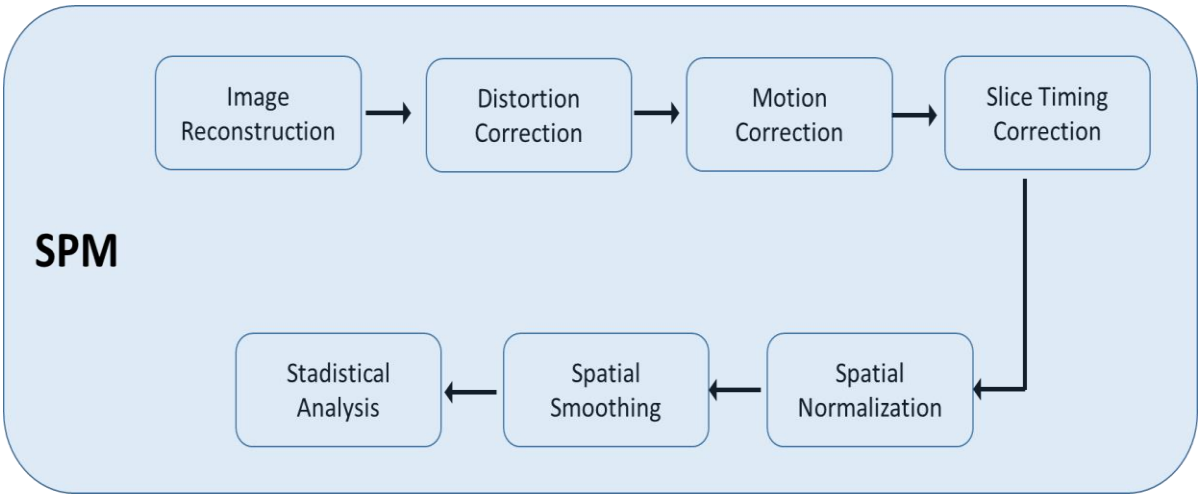

Figure 3: A depiction of common Statistical Parametric Mapping (SPM) processing streams for fMRI data analysis.

1.8 Major components of fMRI analysis.

The analysis of fMRI data is made complex by a number of factors. High image resolution has high sensitivity to motion artifacts and often extends scan time that again magnifies movement artifacts.

The major components of fMRI analysis are meant to deal with each of these problems. The principal components are as follow:

Quality control: Ensuring that the data are not corrupted by artifacts.

Distortion correction: The correction of spatial distortions that often occur in fMRI images.

Motion correction: The realignment of scans across time to correct for head motion.

Slice timing correction: The correction of differences in timing across different slices in each dynamic.

Spatial normalization: The alignment of data from different individuals into a common spatial framework so that their data can be combined for a group analysis.

Spatial smoothing: The intentional blurring of the data in order to reduce noise.

Temporal filtering: The filtering of the data in time to remove low-frequency noise.

Statistical modeling: The fitting of a statistical model to the data in order to estimate the response to a task or stimulus.

Statistical inference: The estimation of statistical significance of the results, correcting for the large number of statistical tests performed across the brain.

Visualization: Visualization of the results and estimation of effect sizes. The goal of this book is to outline the procedures involved in each of these steps.

1.9 Software packages for fMRI analysis

There are a number of comprehensive software packages for fMRI data analysis, each of which has a loyal following (see Table 1).

Table 1: An overview of major fMRI software packages.

Package	Developer	Platform	Licensing
SPM	University College London	MATLAB	Open-source
FSL	Oxford University	UNIX	Open-source
AFNI	National Institute of Mental Health	UNIX	Open-source
Brain Voayager	Brain Innovation	Windows, Linux Mac OS X	Commercial Voyager (closed-source)

In particular, we are going to focus on Statistical Parametric Mapping (SPM), which is the most popular software package for fMRI analysis. SPM was the first widely used and openly distributed software package for fMRI analysis. Developed by Karl Friston (Friston, 2007) and colleagues at University College London, it started as a program for analysis of PET data and was then adapted for analysis of fMRI data. SPM runs over MATLAB (The MathWorks, Natick, MA, USA), which makes it accessible on a very broad range of computer platforms.

The visualization tools available with SPM are relatively limited, and many users take advantage of other packages for visualization.

1.10 The signal processing.

The evoked BOLD response is a complex nonlinear function of neuronal and vascular changes. The shape of the response depends both upon the applied stimulus (i.e. task) and the hemodynamic response to neuronal events. The typical task-based fMRI experiment employs sensory stimuli to cue the participant to perform a behavioral task while BOLD contrast images are acquired for a fixed duration of minutes (Figure 4). Such stimuli can be visual, auditory or of other forms depending on the study.

In all cases, the task design employs a modulation of the brain activity, which will be studied within each scan (state A – experimental and state B – control in Figure 4) so the range of BOLD contrast elicited by the manipulation between experiment and control conditions is captured within the scan.

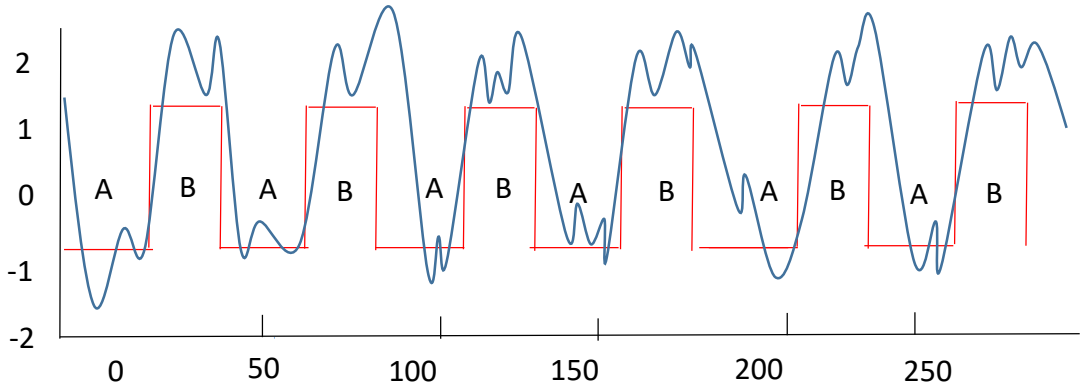

Figure 4:Task-based block design fMRI experiment acquires a time series of images. Time in abscissa and arbitrary values in ordinate.

The BOLD signal (blue) does not increase instantaneously and does not return to baseline immediately after the stimulus ends (red) (Figure 4). Because these changes in blood flow are relatively slow (evolving over several seconds), the BOLD signalis a blurred and delayed representation of the original neural signal.

1.11 Sequences and task/paradigm in fMRI studies.

The choice of the task of stimulation depends on the approach of the study and hypotheses that the scientific wants to test, being able to design both models such as passive task (in which the patient receives a stimulation) and active paradigm (in which the patient must react and provide an answer to a stimulation or an order). Although the vast majority of studies have focused on the use of visual paradigms (Murphy *et al.*, 2003), different paradigms can be applied that affect any sensory input channel, like the auditory paradigm (Martí-Bonmatí *et al.*, 2007; Sanjuan *et al.*, 2007; E.J. Aguilar *et al.*, 2008; Eduardo Jesús Aguilar *et al.*, 2008; Aguilar *et al.*, 2018; Escarti *et al.*, 2019),the olfactory (Schneider *et al.*, 2007) or tactile (Kumari *et al.*, 2003).

1.12 Systematic review and meta-analysis study in FEP applying cognitive and emotional tasks in fMRI.

Ever since the initial neuroimaging studies, there has been strong evidence of brain abnormalities in patients with chronic psychotic disorders (Johnstone *et al.*, 1976). The demonstration by Weinberger (Weinberger *et al.*, 1986) that psychotic patients exhibit less activation of the frontal cortex compared with healthy controls during cognitive tasks has been replicated in several tests of executive functions (Schaufelberger *et al.*, 2005; Reilly *et al.*, 2011; Del Casale *et al.*, 2016; Shafritz *et al.*, 2018). In the last several years, five meta-analyses of fMRI data in patients with chronic psychosis have explored the following: i) executive function (Minzenberg *et al.*, 2009a), ii) emotional face processing (Fusar-Poli *et al.*, 2009) , iii) emotion perception (Kohler *et al.*, 2010) (Kohler et al., 2010) , iv) processing of threatening faces (Dong, Wang, Jia, *et al.*, 2018), and v) resting state (Mwansisya *et al.*, 2017). However, none of these meta-analyses has separately examined individuals with first-episode psychosis (FEP).

It is not well-understood whether the findings in chronic patient populations translate to those with FEP, as the course of illness, long-term use of neuroleptic drugs, extended periods of substance use, and developing psychiatric comorbidities may affect the results.

One of the reasons for the lack of consistency in the results is the difficulty in comparing data, which is due to differences in the homogeneity of the samples and different tasks, unlike the standardization of neuroimaging methodologies and varied statistical analysis. Multivariate patterns of functional disconnectivity across FEP and chronic patients (Li *et al.*, 2017) and a recent systematic review of brain functional changes in task and resting state fMRI revealed impairment of the fronto-temporal pathways to be the core issue in FEP (Mwansisya *et al.*, 2017). These findings are consistent with the classical hypothesis of fronto-temporal dysfunction in chronic patients with schizophrenia (Weinberger *et al.*, 1986).

In turn, the body of the literature on functional brain abnormalities in FEP is subtle and contradictory, exhibiting considerable individual heterogeneity and overlap between FEP patients and controls. Consequently, despite these findings, there are still many questions regarding the patterns of activation according to the fMRI paradigm studies in FEP.

The primary question was whether there were differences in brain activation compared FEP patients and healthy controls using cognitive and emotional paradigms. We hypothesized that FEP patients will have different brain activity compared with healthy controls. We also presumed that the meta-analytic method would be more specific than a systematic review.

To address the gaps in the literature, we conducted a systematic review and a meta-analysis using anisotropic effect-size seed-based mapping (Radua *et al.*, 2014) to investigate the patterns of activation according to the task used during fMRI acquisition in FEP patients versus healthy controls.

1.12.1 Study selection and search strategy.

The systematic review was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations (Moher *et al.*, 2009). We searched PubMed and the Web of Science databases to identify functional neuroimaging studies. The following key terms were used for the query: "(FMRI AND (First episode psychosis))". The automatic searches were accompanied by manually reviewing the references of the eligible articles after the final selection. We identified 704 articles that were published between January 2000 and July 2017.

For inclusion in the systematic review, we considered all original articles written in English that met the following criteria: 1) FEP diagnosis according to criteria from the Diagnostic and Statistical Manual of mental disorders IV (DSM-IV); and 2) task-based fMRI in a cross-sectional case-control design. Studies using resting state and structural MRI modalities were excluded.

Additional exclusion criteria for the meta-analysis were as follows: Region of Interest (ROI) and small volume correction (SVC), studies that did not report quantitative data (coordinates and t-values of the peaks of abnormal brain response), and studies that included participants with >1 acute psychotic episode among the case or control group. Thirty-four studies met the inclusion criteria for the systematic review, and 19 studies met the inclusion criteria for the meta-analysis (Figure 5).

1.12.2 Data extraction for the systematic review.

Two researchers (PSM and GGM) read the full text of each potentially eligible article, and disagreements regarding eligibility criteria were resolved by consensus. The selection of these studies was performed hierarchically (Moher *et al.*, 2009). A primary screening was performed based on title, a second screening was performed based on abstract, and a third screening was performed based on a full text review. When data were either unpublished or incomplete, the corresponding author was contacted and invited to send additional information.

The relevant data of the selected articles were extracted in a predefined structured table (Table 2). The following variables for each article were included in the review: author and year of publication; sample size (FEP patients and controls); sex percentage and mean age of participants; sensory mode; brain function; task fMRI (cognitive or emotional) and a summary of results. In addition, we include two additional tables listing the location and activation of brain areas according to the experimental task applied in the studies (Tables 3 and 4).

1.12.3 Meta-analysis

We conducted the analysis using anisotropic effect-size seed-based mapping (AES-SDM, https://www.sdmproject.com/) (Radua *et al.*, 2014). First, AES-SDM used the coordinates and t-values of the peaks of maximum statistical significance reported in the studies to generate a three-dimensional image of the effect-size of the differences in activation between patients and controls, separately for each study. Specifically, AES-SDM assigned each voxel an effect size that depended on the spatial covariance with the close peaks, of which the effect size was known.

Second, a three-dimensional image of the variance of the effect size was generated again, separately for each study. This step is straightforward because the variance of a given effect size depends only on the effect size and the samples sizes. Third, a standard random-effects meta-analysis was fitted separately for each voxel. Finally, a permutation test for spatial convergence was conducted to detect those regions that showed larger differences between groups compared with most regions (Albajes-Eizagirre *et al.*, 2018).

We also conducted several complementary analyses. First, we extracted the effect sizes of the studies in the meta-analytic peaks to create funnel plots. Funnel plots are useful for detecting potential heterogeneity and publication bias, which we quantitatively assessed with the I^2 statistic and the Egger test, respectively.

To further assess the risk of publication bias, we applied a jack-knife leave-one-out procedure, which consisted of repeating the analysis many times, including all studies but one each time. If a finding was revealed in all iterations, we concluded that we would have detected this region in the meta-analysis even if any of the studies had not been published.

Finally, we repeated all analyses including only studies that used cognitive tasks. We used a composite threshold for statistical significance (uncorrected voxel $p < 0.001$, peak SDM-Z value > 2, plus cluster extent > 100 voxels), which is more conservative than the recommended threshold for SDM (Radua *et al.*, 2012) (see Table 5).

1.12.4 Results in the systematic review.

A total of 704 records were identified through database searching. Out those records, 34 articles met the eligibility criteria (Figure 5 for PRISMA flow diagram). The pooled sample size in the FEP group was n=763 patients, the mean age was 24 years old (range 20 to 31), 30% of subjects were females, and 80% received antipsychotic medication.

These parameters were matched to a healthy control group with a sample size of n=760 and a mean age of 25 years old (range 20 to 34 years old), and 46% of the subjects were females. The subgroup with cognitive task fMRI data included a sample size of n=662 and a mean age of 24 years old (range 20 to 31 years-old), and 23% of the subjects were female.

This subgroup was matched with 644 healthy controls with a mean age of 25 years old (range 20 to 34 years old), among which 31% of the subjects were female.

The subgroup with emotional task fMRI data included a sample size of n=101 and a mean age of 26 years old (range 23 31 years old); among these subjects, 37% were female. This subgroup was matched with 116 healthy controls with mean age of 26 years old (range 24 to 31 years-old); among the controls, 26% were female.

The included studies demonstrated reduced activation of the temporal lobe, parietal lobe, frontal lobe and limbic areas (Braus *et al.*, 2000, 2002; Achim *et al.*, 2007; Fusar-Poli *et al.*, 2007; Van Veelen *et al.*, 2011; Fornito *et al.*, 2011; Smieskova *et al.*, 2012; Yoon *et al.*, 2012; Esslinger *et al.*, 2012; Villalta-Gil *et al.*, 2013; Kambeitz-Ilankovic *et al.*, 2013; Lesh *et al.*, 2013; Bergé *et al.*, 2014; Benetti *et al.*, 2015; Schmidt *et al.*, 2016; Tseng *et al.*, 2016) as well as the basal ganglia (Raij *et al.*, 2015) and cingulated cortex (Reske *et al.*, 2009) in FEP patients compared with healthy controls. In contrast, five studies reported increased activation in the ventro-lateral prefrontal cortex (VLPFC) (Tan *et al.*, 2005; Schneider *et al.*, 2007; Bendfeldt *et al.*, 2015; Hawco *et al.*, 2015; Vogel *et al.*, 2016).

In addition, there were nine studies that showed reduced and increased activation in different brain regions, including the frontal and prefrontal cortex, insula, temporal lobe, occipital lobe, thalamus and limbic system (Boksman *et al.*, 2005; Tan *et al.*, 2005; Fusar-Poli *et al.*, 2007; Schneider *et al.*, 2007; Bleich-Cohen *et al.*, 2009; Reske *et al.*, 2009; Woodward *et al.*, 2009; Lencer *et al.*, 2011; Reilly *et al.*, 2011; Guerrero-Pedraza *et al.*, 2012) in Table 2.

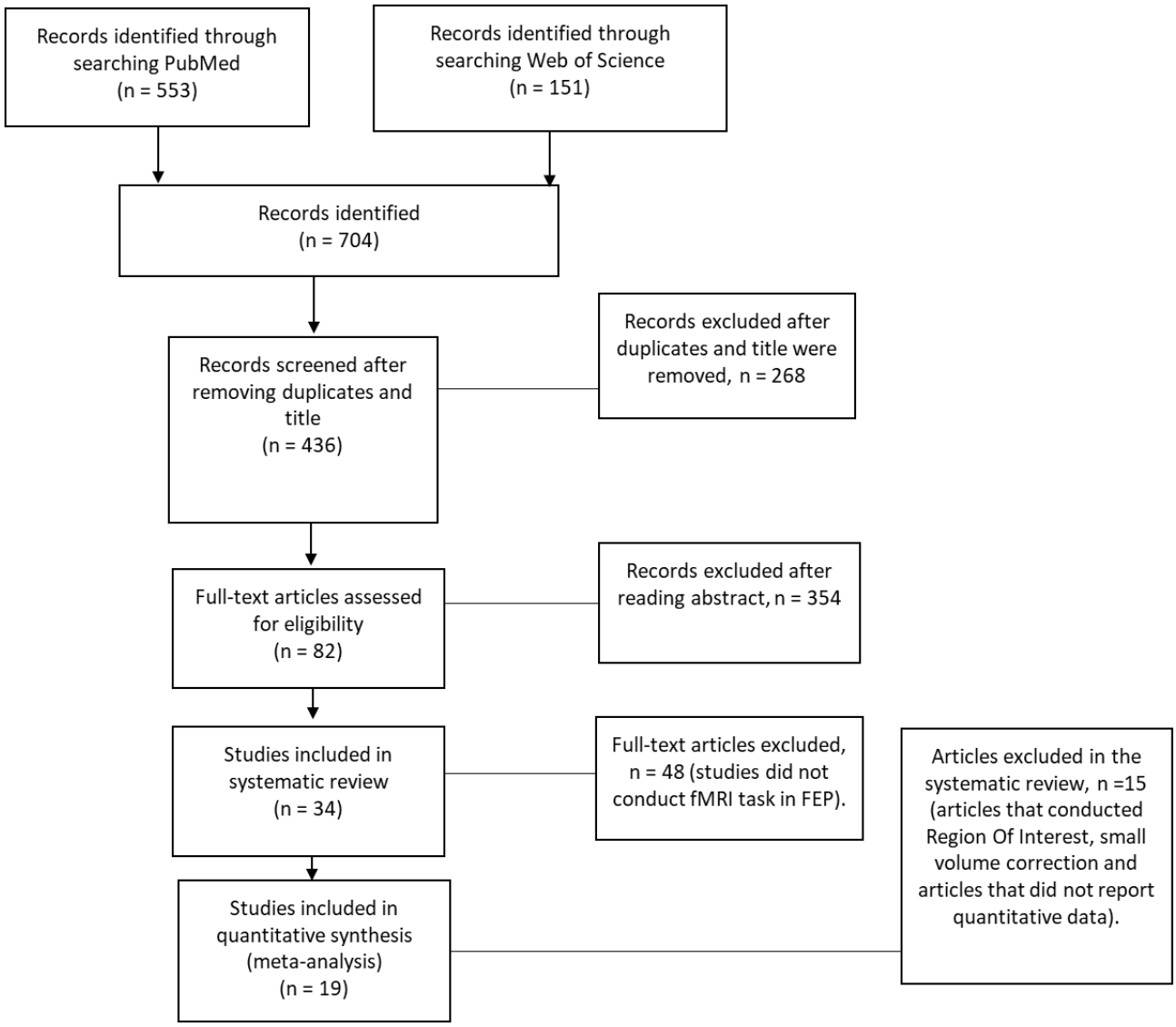

Figure 5:Prisma Flow diagra of study selection.

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Table 2:Systematic review studies using fMRI in FEP

Author	*Year*	*First Episode Patients*			*Controls*			*Sensory mode*	*Brain Function*	*Task fMRI*	*Summary of results*
		N	*M/F*	*Mean age*	*N*	*M/F*	*Mean age*				
Braus et al	2000	12	6/6	25	12	6/6	28	Visual and motor	Repetitive sequential Finger	Cognitive and motor	Reduce in motor cortical dysfunction
Braus et al	2002	12	6/6	25	11	6/5	29	Auditory and visual	Visual and auditory simultaneous	Cognitive	Reduce in right thalamus, LSTG, and parietal lobe.
Boksman et al	2005	10	9/1	22	10	9/1	23	Visual	Verbal fluency	Cognitive	Reduce DLPFC, left STG. Increase LFL, right anterior cingulate, thalamus, insula, IFL, IOG and FG
Tan et al	2005	11	5/6	25	11	5/6	26	Visual verbal motor	Working memory	Cognitive	Reduce bilateral DLPFC. Increase VLPFC
Schneider et al	2007	48	26/22	31	57	31/26	31	Visual	Working memory	Cognitive	Reduce STG, thalamus. Increase VLPFC
Bleich-Cohen et al	2007	12	6/6	27	17	10/7	34	Auditory verbal motor	Verbal Fluency	Cognitive	Reduce LIFG and Wernicke. Increase RSTS
Achim et al	2007	26	18/8	22	20	11/9	23	Visual verbal motor	Encoding strategies	Cognitive	Reduce bilateral MTG.
Fusar-Poli et al	2007	10	10/-	25	NONE			Visual	Verbal Fluency	Cognitive	Reduce DLPFC, thalamus and FPC Increase VLPFC

Benetti et al	2009	10	7/3	25	14	9/5	26	Visual	Encoding strategies, maintenance and recognition	Cognitive	Increase in encoding SPG, SMG. In maintenance bilateral anterior insula, right anterior cingulate. In recognition Bilareral (IFG and STG), right insula and MTG
Crossley et al	2009	10	7/3	25	13	9/5	26	Visual	Working memory	Cognitive	Increase in STL and MFG
Reske et al	2009	18	10/8	31	18	10/8	31	Visual verbal motor	Emotion discrimination	Emotional	Reduce Anterior cingulate and orbitofrontal. Increase Posterior cingulate and precuneus
Woodward et al	2009	15	12/3	22	32	22/10	22	Visual	Choice reaction time	Cognitive	Increase Right MFG, right SMA and left MFG.
Fornito et al	2011	23	14/9	20	25	12/13	22	Visual	Working memory	Cognitive	Reduce Cingulate and frontoparietal
Lencer et al	2011	40	26/14	24	20	10/10	24	Visual	Visual motion processing	Cognitive	Reduce Intraparietal suculus, DLPFC. Increase Dorsomedial thalamus and insula.
Purdon et al	2011	17	13/4	21	17	13/4	22	Visual	Serial reaction time	Cognitive	Reduce Bilateral MFG Striatum-thalamus-cortical circuits. Increase Left STG
Van Veelen et al	2011	23	23/-	25	33	33/-	24	Visual	Working memory	Cognitive	Reduce Left IFG and left STG.
Guerrero-Pedraza et al	2012	30	21/9	26	28	20/8	27	Visual	Working memory	Cognitive	Reduce Medial frontal cortex, thalamus and posterior cingulate. Increase DLPFC, VLPFC, anterior insula.
Esslinger et al	2012	27	20/7	28	27	20/7	27	Visual	Face marching	Emotional	Reduce VS, orbitofrontal cortex, precuneus

Smieskova et al	2012	21	16/5	28	20	10/10	26	Visual	Working memory	Cognitive	Reduce Bilateral precuneus, and bilateral IFG, LIFG and Insula
Yoon et al	2012	51	39/12	20	51	-/-	20	Visual	Attentional processing	Cognitive	Reduce DLPFC
Kambeitz-Ilankovic et al	2013	20	14/6	25	20	14/6	26	Visual	Attentional processing	Cognitive	Reduce Right MTG, and left precuneus
Lesh et al	2013	43	34/9	28	54	35/19	---	Visual	Attentional processing	Cognitive	Reduce DLPFC and parietal
Schmidt et al	2013	21	14/6	25	20	14/6	26	Visual	Working memory	Cognitive	Reduce Right MFG and superior parietal lobe
Villata-Gil et al	2013	20	13/7	23	31	20/11	25	Visual	Emotional discrimination	Emotional	Reduce right middle cingulate,
Berge et al	2014	18	9/9	24	19	10/9	24	Visual	Emotional discrimination	Emotional	Reduce Amygdala, posterior ventral areas, thalamus, IFG and MTG
Benetti et al	2015	46	27/19	25	22	11/11	-----	Auditory	Verbal fluency	Cognitive	Reduce LIFG and left MTG. Increase MTG and bilateral VLPFC inferior
Bendfeld et al	2015	19	-/-	----	19	-/-	----	Visual	Working memory and verbal fluency	Cognitive	Reduce Cerebellum, FG and DLPFC. Increase VLPFC and IFG
Buchy et al	2015	25	20/5	24	24	-/-	---	Visual	Memory	Cognitive	Increase VLPFC
Hawco et al	2015	26	22/4	24	24	19/5	----	Visual	Memory	Cognitive	Increase Caudate, cingulate, suculus, FG and VLPFC

Keedy et al	2015	21	16/5	23	21	10/11	24	Visual	Attentional processing	Cognitive	Reduce SFG, bilateral insula, right SMG, and bilateral, ILC, DLPFC. Increase Before treatment DLPFC
Raij et al	2015	30	18/12	27	30	24/6	29	Visual	Attentional processing	Cognitive	Reduce Putamen
Schmidt et al	2016	29	19/10	24	19	10/9	26	Visual	Reward task.	Cognitive	Reduce Ventral tegmental area, insula, anterior cingulate cortex
Tseng et al	2016	18	-/-	27	21	-/-	----	Visual	Face matching	Emotional	Reduce Left amygdala, STG, medial orbitofrontal gyrus, LG, left dorsal caudate and AG.
Vogel et al	2016	22	22/-	28	20	7/13	22	Visual	Working memory	Cognitive	Increase Prefrontal cortex in Superior frontal gyrus and (after medication VLPFC)

AG= Angular Gyrus, CPT= Continuous Performance Test, DLPFC= Dorso lateral prefrontal cortex, FG= Fusiform gyrus, FPC= Frontal Posterior Cingulate, HPC= Hippocampus , IFG= Inferior Frontal Gyrus, IFG= Inferior Frontal Gyrus, IFL= Inferior frontal lobe, ILC= Inferior Lingual Cortex, IOG= Inferior occipital gyrus, LFL= Left Frontal Lobe, LG= Lingual Gyrus, LIFG= Left Inferior Frontal Gyrus, LSTG= Left Superior Temporal Gyrus, LTG= Left temporal Gyrus, MFG= Middle Frontal Gyrus, MOFG= Medial Orbitofrontal gyrus, MTG= Middle Temporal Gyrus, RSTS= Right Superior Temporal Suculus, SFG= Superior Frontal Gyrus, SMA= Supplementary motor area, SMG= Supramarginal gyrus, SPG= superior parietal gyrus, STG= Superior Temporal Gyrus, STL= Superior temporal lobe, VLPFC= Ventro lateral prefrontal cortex, VS= Ventral Striatal.

Three out of 34 studies used different types of auditory function in the cognitive task (one study used an auditory-visual task, one study used an auditory-verbal task, and one study used only auditory function). A total of 29 studies used visual function, and two studies used a visual-verbal task (see Table 2). To explore the influence of the emotional tasks, most of the studies examined not only the role of the amygdala and hippocampus but also the frontal cortex and superior temporal lobe (see Table 3).

Twenty-nine of the studies (see Table 2) used a cognitive task; of these, 32% were working memory tasks, 12% were verbal fluency tasks, 9% were assessments of attention (continuous performance tasks), 6% were alternating visual and acoustic stimulus, 6% were encoding strategies, 6% were memory tasks, 6% were visual motor processing tasks and 3% were serial reaction time (SRT), repetitive sequential finger and reward tasks. The remaining five studies (Table 3) implemented emotional tasks (Reske *et al.*, 2009; Esslinger *et al.*, 2012; Villalta-Gil *et al.*, 2013; Bergé *et al.*, 2014; Tseng *et al.*, 2016) using visual stimuli; 15% (of all tasks) were emotion discrimination, and 5% were face matching.

Table 3:Systematic review studies using fMRI cogntive paradigm in FEP.

Study Name	Year	Cognitive task	Sensory mode	FL		DLPFC		VLPFC		TL		PL		Cingulate		Insula		Putamen		Thalamus	
				Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side
Braus et al	2000	Repetitive sequential finger	Visual	-	-	-	-	-	-	-	-	↓	-	-	-	-	-	-	-	-	-
Braus et al	2002	Visual and auditory simultaneous	Auditory visual			-	-	-	-	↓	L	↓	-	-	-	-	-	-	-	↓	R
Boksman et al	2005	Verbal fluency	Visual	↑	L	↓	-	-	-	↓	L	-	-	↑	A	↑	R	-	-	↑	R
Tan et al	2005	Working memory	Visual	-	-	↓	B	↑	-	-	-	-	-	-	-	-	-	-	-	-	-
Schneider et al	2007	Working memory	Visual	-	-	-	-	↑	-	↓	-	-	-	-	-	-	-	-	-	↓	-
Bleich-Cohen et al	2007	Verbal fluency	Auditory verbal	↓	L	-	-	-	-	-	-	↑	R	-	-	-	-	-	-	-	-
Achim et al	2007	Encoding strategies	Visual verbal	-	-	-	-	-	-	↓	M	-	-	-	-	-	-	-	-	-	-
Fusar-Poli et al	2007	Verbal fluency	Visual	-	-	↓	-	↑	-		-	-	-	↓	P	-	-	-	-	↓	-
Benetti et al	2009	Encoding strategies, maintenance and recognition	Visual	↑	I	-	-	-	-	↑	B	-	-	↑	R	↑	A	-	-	-	-
Crossley et al	2009	Working memory	Visual	↑	M	-	-	-	-	↑	S	-	-	-	-	-	-	-	-	-	-
Woodward et al	2009	Choice reaction time	Visual	↑	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fornito et al	2011	Working memory	Visual	↓	-	-	-	-	-	-	-	↓	-	↓	-	-	-	-	-	-	-
Lencer et al	2011	Visual motion processing	Visual	-	-	↓	-	-	-	-	-	-	-	↓	-	↑	-	-	-	↑	-

Purdon et al	2011	Serial reaction time	Visual	-	-	-	-	-	-	↑	L	-	-	-	-	-	-	-	-	↓	-
Van Veelen et al	2011	Working memory	Visual	↓	L	-	-	-	-	↓	-	-	-	-	-	-	-	-	-	-	-
Guerrero-Pedraza et al	2012	Working memory	Visual	↓	M	↑	R	↑	R	-	-	-	-	↓	P	↑	A	-	-	↓	-
Smieskova et al	2012	Working memory	Visual	↓	B	-	-	-	-	-	-	↓	-	-	-	↓	-	-	-	-	-
Yoon et al	2012	Attentional processing	Visual	-	-	↓	-	-	-	↓	-	↓	-	-	-	-	-	-	-	-	-
Kambeitz-Ilankovic et al	2013	Attentional processing	Visual	-	-		-	-	-	↓	-	↓	-	-	-	-	-	-	-	-	-
Lesh et al	2013	Attentional processing	Visual	-	-	↓	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schmidt et al	2013	Working memory	Visual	↓	R	-	-	-	-	-	-	↓	-	-	-	-	-	-	-	-	-
Benetti et al[25]	2015	Verbal task	Auditory	↓	L		-	↑	-	↓	L	-	-	-	-	-	-	-	-	-	-
Bendfeld et al	2015	Working memory and verbal fluency	Visual	↑	-	↓	-	↑	-	-	-	-	-	-	-	-	-	-	-	-	-
Buchy et al	2015	Memory	Visual	-	-	-	-	↑	-	-	-	-	-	-	-	-	-	-	-	-	-
Hawco et al	2015	Memory	Visual	-	-	-	-	↑	-	-	-	-	-	↑	-	-	-	-	-	-	-
Keedy et al	2015	Attentional processing	Visual	↓	S	-	-	-	-	-	-	-	-	-	-	↓	-	-		-	-
Raij et al	2015	Attentional processing	Visual	-	-	-	-	-	-	-	-	-	-	↓	-	↓	-	↓	-	-	-
Schmidt et al	2016	Reward task	Visual	-	-	-	-	-	-	-	-	-	-	↓	A	↓	-	-	-	-	-
Vogel et al	2016	Working memory	Visual	↑	-	-	-	↑	-	-	-	-	-	-	-	-	-	-	-	-	-

A= Anterior, **B**= Bilateral, **DLPFC**= Dorso lateral prefrontal cortex**, FL**= Frontal lobe, **I**= Inferior **L**= Left side, **M**= Medial, **P**= Posterior, **PL**= Parietal lobe, **R**= Right side, **S**= Superior,

TL= Temporal lobe, **VLPFC**= Ventro lateral prefrontal cortex.

↑ **Increased activation** ↓ **Reduced activation**

Table 4:Systematic review studies using fMRI emotional paradigm in FEP.

Study Name	Year	Emotional task	Sensory mode	Amygdala		BG		FL		TL		Cingulate		Insula		Thalamus	
				Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side	Activity	Side
Reske et al[37]	2009	Emotion discrimination	Visual verbal	-	-	-	-	↓	OBF	-	-	↓ ↑	A, P	-	-	-	-
Esslinger et al[34]	2012	Face marching	Visual	-	-	↓	VS	↓	OBF	-	-	-	-	-	-	-	-
Vilata-Gil et al[35]	2013	Emotional discrimination	Visual	-	-	-	-	-	-	-	-	↓	R	-	-	-	-
Berge et al[49]	2014	Emotional discrimination	Visual	↓	P	-	-	↓	-	↓	-	-	-	-	-	↓	-
Tseng et al[27]	2016	Face matching	Visual	↓	L	↓	L,C	↓	OBF	↓	S	-	-	-	-	-	-

A= Anterior, **C**= Caudate, **BG**= Basal Ganglia, **FL**= Frontal lobe, **L**= Left side, **OBF**= Orbitofrontal, **P**= Posterior, **PL**= Parietal lobe, **S**= Superior, **TL**= Temporal lobe, **VS**= Ventral Striatal.

↑ **Increased activation** ↓ **Reduced activation**

Table 5:Results of the meta-analysis.

	Peak					Cluster	
	x,y,z	SDM-Z	*P*	I^2	Egger	Extent	Breakdown (voxels)
Patients > controls							
(no findings)							
Patients < controls							
L precuneus	-12,-64,58	-3.2	5e-06	0%	n.s.	362 voxels	L precuneus, mainly BA 7 (276) L superior parietal gyrus, mainly BA 7 (55)
L anterior insula	-36,18,-12	-3.1	1e-05	0%	n.s.	437 voxels	L insula, mainly BA 47 (178) L putamen (84) L inferior frontal gyrus, mainly BA 47 (78)
Median cingulate cortex	4,26,40	-2.4	7e-4	82 %	*P*=0.002	157 voxels	B superior frontal gyrus, mainly BA 32 (62) B supplementary motor area, mainly BA 8 (54) B median cingulate cortex, mainly BA 32 (24) B anterior cingulate cortex, mainly BA 32 (17)

*Coordinates are in Montreal Neurological Institute (MNI) space.

B: bilateral; BA: Brodmann area; L: left; R: right.

As indicated in (Tables 2 and 3), the most significant finding in the systematic review between task fMRI and brain areas was found in the prefronto-temporal pathways (Braus *et al.*, 2000; Tan *et al.*, 2005; Achim *et al.*, 2007; Schneider *et al.*, 2007; Fusar-Poli *et al.*, 2007; Benetti *et al.*, 2009; Crossley *et al.*, 2009; Lencer *et al.*, 2011; Purdon *et al.*, 2011; Van Veelen *et al.*, 2011; Fornito *et al.*, 2011; Smieskova *et al.*, 2012; Yoon *et al.*, 2012; Esslinger *et al.*, 2012; Guerrero-Pedraza *et al.*, 2012; Kambeitz-Ilankovic *et al.*, 2013; Lesh *et al.*, 2013; McFarland *et al.*, 2013; Bergé *et al.*, 2014; Bendfeldt *et al.*, 2015; Hawco *et al.*, 2015; Keedy *et al.*, 2015; Tseng *et al.*, 2016) Interestingly, activity appears to be decreased in the left inferior frontal gyrus (LIFG) (Bleich-Cohen *et al.*, 2009; Van Veelen *et al.*, 2011; Benetti *et al.*, 2015), bilateral middle frontal gyrus (MFG) (Purdon *et al.*, 2011), orbital frontal gyrus (Reske *et al.*, 2009; Esslinger *et al.*, 2012; Tseng *et al.*, 2016), amygdala (Bergé *et al.*, 2014; Tseng *et al.*, 2016), precuneus (Esslinger *et al.*, 2012), superior parietal lobe (SPL) (Schmidt *et al.*, 2013) and thalamus (Braus *et al.*, 2002; Fusar-Poli *et al.*, 2007; Schneider *et al.*, 2007; Guerrero-Pedraza *et al.*, 2012; Bergé *et al.*, 2014) in FEP patients compared with the controls.

However, a number of studies reported an increased task-related BOLD activity in the insula (Benetti *et al.*, 2009; Lencer *et al.*, 2011; Guerrero-Pedraza *et al.*, 2012), cingulate (Boksman *et al.*, 2005; Benetti *et al.*, 2009; Reske *et al.*, 2009) and thalamus (Boksman *et al.*, 2005; Lencer *et al.*, 2011) of patients with FEP compared with the controls. Tan et al. (Tan *et al.*, 2005) reported reduced bilateral activation in the DLPFC and increased bilateral activation in the VLPFC.

Another study described increased activity in the DLPFC, VLPFC, and anterior insula (Guerrero-Pedraza *et al.*, 2012), whereas the medial frontal cortex, thalamus and cingulate showed reduced activation during cognitive tasks. In line with these findings, one functional study showed that chronic patients performed significantly worse than FEP patients during tasks involving a higher load working memory. The same study showed higher activation in the VLPFC and the left superior frontal gyrus (SFG) (Vogel *et al.*, 2016).

An Ontario group (Boksman *et al.*, 2005) showed that never-treated FEP patients exhibited relatively lower activation in the prefrontal and anterior cingulate while conducting the word fluency task. Further, (Bleich-Cohen *et al.*, 2009) explored brain region activation using an auditory task based on language tasks. This group reported reduced activation in the left inferior frontal gyrus in FEP patients compared with healthy controls. In contrast, the right superior temporal suculus (RSTS) exhibited increased activity in FEP patients (Fusar-Poli *et al.*, 2007).

Achim et al.(Achim *et al.*, 2007) examined encoding strategies and detected reduced activation in the bilateral medial temporal lobes in FEP patients compared to healthy controls.

Another study examined prefronto-hippocampal activity and demonstrated that FEP patients exhibited greater activation in the inferior frontal gyrus, superior temporal gyrus (SGT), cingulate, and right insula compared with the healthy controls (Benetti *et al.*, 2009).

Yoon et al. (Yoon *et al.*, 2012) reported decreased activation in the DLPFC, suggesting that neurophysiological markers of illness may not be as evident in FEP patients as they are in patients with more established illness. In addition, Lesh et al. (Lesh *et al.*, 2013) determined that FEP patients exhibited reduced activity in the DLPFC and inferior parietal cortex, whereas the healthy controls did not exhibit such a reduction. In contrast, in a study of patients after treatment, Keedy et al. (Keedy *et al.*, 2015) reported a significant increase in the activity in the DLPFC similar to that shown in the healthy controls. Another study reported that putamen signaling was reduced in the patient group, and the degree of this alteration was positively correlated with delusion scores and negatively correlated with the antipsychotic equivalent dose (Raij *et al.*, 2015), which was in accordance with the dysfunction of striate-cortical connectivity (Fornito *et al.*, 2011).

With respect to emotional task findings, one study showed reduced brain activity during facial emotion discrimination (Reske *et al.*, 2009), underlying functional deficits in the anterior and posterior cingulate cortex (Habel *et al.*, 2004).

Interestingly, one study using visual tasks showed significant differences in the right cingulate during facial emotional processing between FEP patients and healthy controls (Villalta-Gil *et al.*, 2013).

However, another study that also used an active emotional task, including a visual task, reported reduced activation in FEP patients in the amygdala, ventro-limbic regions, thalamus, frontal and temporal regions when discriminating emotions, compared with the healthy control group (Bergé *et al.*, 2014).

In this context, reduced activation was found in FEP patients in the left amygdala, superior temporal gyrus, and medial orbital frontal gyrus. These abnormalities were associated with emotion recognition during a dynamic facial task and prosodic voice stimuli (Tseng *et al.*, 2016).

1.12.5 Results of Meta-analysis

In the pooled analysis of studies that used a cognitive task, patients with FEP exhibited significantly decreased activation in left precuneus (peak in Brodmann area 7) and left anterior insula (peak in Brodmann area 47), as shown in Figure 7. We did not observe outliers or asymmetry in the funnel plots of their peaks, and we detected these results in all jack-knife analyses when we restricted the meta-analysis to studies using cognitive tasks (n=14) and in all jack-knife analyses of the meta-analysis restricted to studies using cognitive tasks (Figure 6).

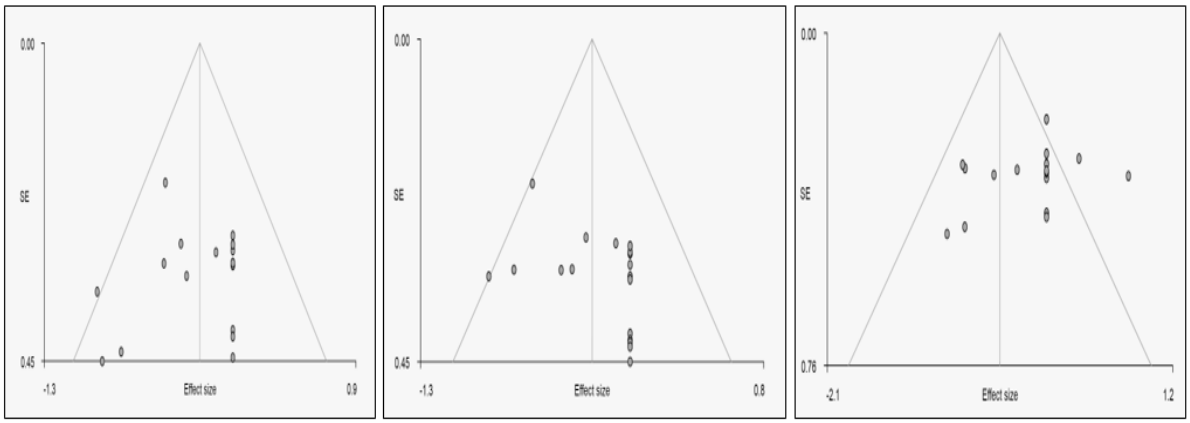

Figure 6:Funnel plot and its peak (from the left to the right) left insula BA47, left precuneus BA7 and Right median cingulate / paracingulate gyri, BA 32.

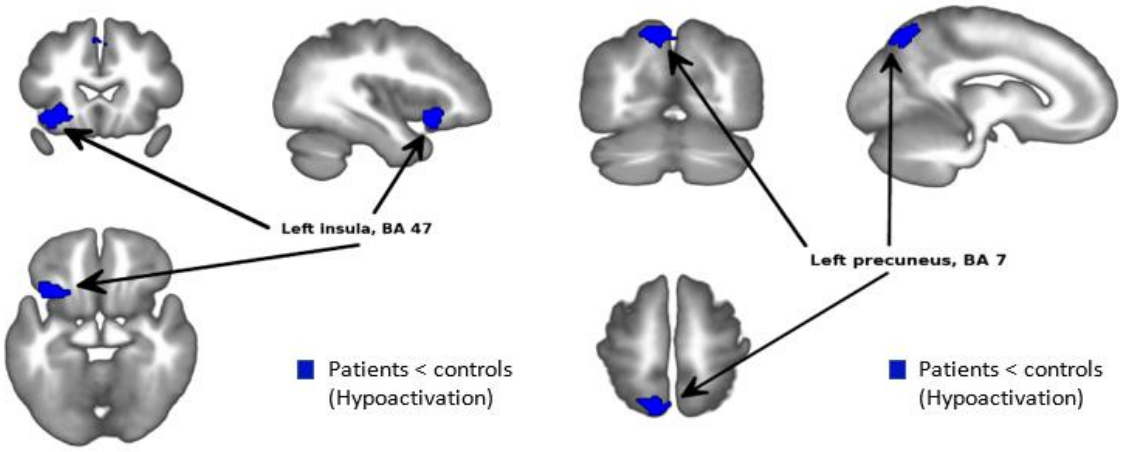

Figure 7:Cognitive brain responses abnormalities in functional paradigm. (from left to right) left insula and left precuneus.

Among the studies that used an emotional task, patients also exhibited decreased activation in the right median cingulate cortex (peak in Brodmann area 32), and we detected this finding in all jack-knife analyses (Figure 8). However, this finding was less pronounced, and it was less significant; the funnel plot of its peak showed serious heterogeneity (I^2 = 82%) and asymmetry (Table 5), indicating potential publication bias (Egger test p = 0.002).

Moreover, we did not detect this abnormality when we restricted the meta-analysis to studies using cognitive tasks. We did not detect significantly increased activation or failure to deactivate.

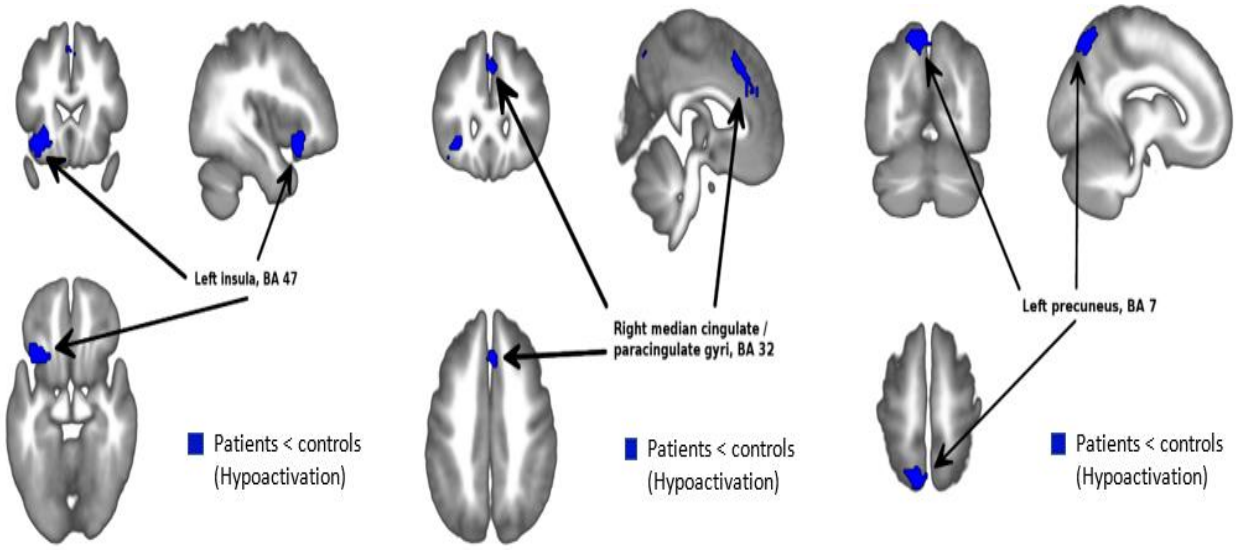

Figure 8: Meta-analyses of functional abnormalities

1.12.6 Discussion of the systematic review and meta-analysis

To the best of our knowledge, this report describes the first systematic review and meta-analysis of studies comparing brain activity between FEP patients and healthy controls using task-based fMRI. The primary findings of the systematic review revealed that there are many involved brain areas (DLPFC, frontal lobe, thalamus, cingulate, amygdala, precuneus and insula), which suggests brain abnormalities in FEP patients.

This interpretation is consistent with the classical model of fronto-temporal abnormality as a key issue in schizophrenia (Kraepelin, 1921; Weinberger *et al.*, 1986; Andreasen *et al.*, 1992).

This finding is also in accordance with previous meta-analytic findings on altered frontal activation in chronic patients (Minzenberg *et al.*, 2009b) and with a recent study comparing fMRI of FEP patients with chronic patients (Li *et al.*, 2017).

However, our meta-analysis did not reveal significant differences in frontal lobe activity between FEP patients and healthy controls. Our results showed robust differences in only three brain areas with decreased functional activity (the right cingulate, left insula and left precuneus). These differences in the results between individual studies and the meta-analysis highlight the important effect of methodological differences between studies; as more studies were included, more brain areas appeared to be significantly different between groups. The number of studies included in the systematic review (n=34) is larger than in the meta-analysis (N=19). However, this finding is not observed in fMRI studies in patients with chronic psychosis. A meta-analysis of 41 fMRI studies on executive function in patients with schizophrenia showed altered activity primarily in the DLPFC (Minzenberg *et al.*, 2009b).

According to our meta-analytical findings, these latter abnormalities are not observed early in the course of illness. Assuming that the meta-analysis, as a set of quantitative procedures, generates conclusions that are more accurate, reliable and more rigorous than those generated from any single study or a non-quantitative review (Rosenthal *et al.*, 2001).

We hypothesized that frontal lobe abnormalities are secondary to many factors but are not the core issue of psychosis. In accordance with our findings, a recent meta-analytic study of connectivity from 52 resting-state fMRI studies revealed that hyper-connectivity between the affective network (AN, emotion system) and the ventral attention network (VAN, salience processing system), which was associated with deficits in emotion, perception and behavioral regulation, was the core abnormality in psychosis (Dong, Wang, Chang, *et al.*, 2018). The present meta-analyses of all 19 studies indicated that the insula is the most clearly affected area in FEP patients. The insula is a brain area with wide effects on numerous parts of the limbic system, which is involved in the evaluative and experimental aspects of internally generated emotions (Craig, 2002; Palaniyappan *et al.*, 2011). The insula integrates external sensory input with the limbic system (Mallikarjun *et al.*, 2018). A meta-analysis of fMRI studies with insula activation (Kurth *et al.*, 2010) propose that the insula is concerned with an integrateive process. This integration of different qualities of our coherent knowledge of the world set the framework for thoughts and actions.

Many deficits reported in psychosis include insula functions, which may be associated with altered processing of emotions, visual and representations of the self (Radua *et al.*, 2010). This reduction in activity was also observed in antipsychotic-naive patients (Keedy *et al.*, 2015; Wei *et al.*, 2016).

In contrast, several studies reported increased activation in the insula during different cognitive tasks (Boksman *et al.*, 2005; Benetti *et al.*, 2009; Lencer *et al.*, 2011; Guerrero-Pedraza *et al.*, 2012; Del Casale *et al.*, 2016) and, interestingly, during a self-reference task (Girard *et al.*, 2017).

Conversely, there are few longitudinal studies of FEP using fMRI. In a systematic review of this issue (González-Vivas *et al.*, 2019), we showed that most studies reported a hypo-activation in the limbic system, hippocampus, striatum and prefrontal cortex at base-line. At follow-up, almost all studies reported normalization of the activation levels in these regions. Thus, one advantage of using fMRI is its potential to serve as a bio-marker for predicting the response to pharmacological or psychotherapeutic treatment (Gong *et al.*, 2016; Kani *et al.*, 2017; Aguilar *et al.*, 2018). Despite these results, fMRI is not used in clinical practice as a predictor of treatment response.

The other main area implicated in the meta-analysis was the precuneus, which in healthy controls, has been linked to the subjective experience of emotion (Terasawa *et al.*, 2013). In schizophrenic patients, greater precuneus perfusion was observed in patients with preserved insight compared with patients with impaired insight (Faget-Agius *et al.*, 2012).

Recently, there has been evidence of a deficit for actively binding information in working memory (Grot *et al.*, 2017). Using machine learning techniques to differentiate first-episode patients, voxels with the best classification were clustered in a bilateral region of the precuneus (Rikandi *et al.*, 2018).

Finally, our meta-analysis identified the right median cingulate cortex and paracingulate gyri as being altered in FEP, which is in line with several studies that have provided evidence for disruption in the cingulate, which was associated with impairments in cognitive and emotional functions (Baiano *et al.*, 2007; Picó-Pérez *et*

al., 2017). However, other studies have not observed such disruption in the cingulate cortex (Boksman *et al.*, 2005; Benetti *et al.*, 2009; Reske *et al.*, 2009; Hawco *et al.*, 2015). It is worth noting that when we excluded emotional task studies in the meta-analysis, the cingulated cortex failed to produce significant results.

1.12.7 Role of methodological differences in the comparability of results across the studies.

The hardware of the MR equipment, including the type, manufacturer, coils and acquisition sequences is an important source of bias that is necessary to consider. The external magnetic field is directly related to the blood oxygenation level-dependent (BOLD) signal (Meindl *et al.*, 2008). A stronger magnetic field results in a greater BOLD signal.

In a typical block-design fMRI acquisition, the averaged raw signal difference due to susceptibility effects between activated and not-activated dynamics is approximately 1% greater in 3 vs 1.5 Tesla magnets (Krüger G, Kastrup A, 2001). Another source of variability between the relevant activated areas in FEP is the post-processing method used for obtaining the fMRI resulting maps. The most common fMRI software packages, such as SPM (including different versions SPM99, SPM5 and SPM8) (Friston, 2007), Brainvoyager (Goebel *et al.*, 2006) and FSL (Jenkinson *et al.*, 2012), include different recommendations regarding the default values for the registration, normalization, filtering, or smoothing steps, which largely affects the final parametric maps of activation (Tahmasebi *et al.*, 2009; Molloy *et al.*, 2014; Chen *et al.*, 2018).

SPM was the most commonly used software in the studies that were included in this meta-analysis, and SPM has slightly higher sensitivity than the other methods (Morgan *et al.*, 2007), especially when the realignment parameters calculated from motion head correction are estimated and included as a statistical regression in the general lineal model design matrix. Unfortunately, the full list of parameters, thresholds, and critical values are not usually included in the methods section of the published papers; thus, many of these parameters cannot be clearly considered and analyzed separately in the systematic review and meta-analysis, which contributes to a confounding effect when considering relevant areas in FEP fMRI studies.

Our meta-analytic results show that the insula and precuneus primarily display reduced activation that may be associated with salience attribution to external stimuli and related to the deficits in perception and regulation (Kapur, 2003; Wylie *et al.*, 2010; Palaniyappan *et al.*, 2012; Dong, Wang, Jia, *et al.*, 2018).

In support of our hypothesis, the available data from the meta-analysis indicate that FEP patients have reduced brain activation abnormalities compared with healthy controls. In particular, abnormal activation in the prefrontal and frontal lobes are not present at the illness onset. The classical finding of frontal lobe dysfunction in many studies may be secondary to either insula dysfunction or changes that occur in the progression of the illness. The inconsistent findings between the systematic review and meta-analysis suggest that methodology factors, such as the type of task, number of studies included, environmental factors, clinical, medication, and technical procedures, are key factors that may explain the paradoxical results.

In this regard, further studies using the same easily replicable fMRI paradigms with identical technical procedures in larger samples are warranted to obtain clear conclusions regarding brain abnormalities in FEP patients.

A wide range of neuroimaging paradigms have been used to study brain abnormalities in FEP patients. Most of the studies have used different sensory modalities, in particular, visual sensory modality through the recognition of facial emotions and cognitive paradigms. However, relatively few of them have used emotional processing with the auditory modality, despite the importance of language in human emotions.

Thus, the main objective of this Thesis is to analyze and provide evidence linking the auditory emotional paradigm with brain activation among FEP patients because until today this auditory paradigm had not yet been used in FEP patients.

In this line, this study provides a continuity to the project that started in 2005 with the development of the auditory emotional paradigm, and two years later with the first publication (Sanjuan *et al.*, 2007) using the auditory paradigm which was applied to evaluate cerebral activation with fMRI in patients with chronic schizophrenia and healthy controls.

2. HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

H1: There will be statisitcal significant differences in brain activation between FEP patients and HCs in fMRI when hearing the emotional auditory paradigm.

The specific hypotheses that emerge from the H1 are:

H1.1: FEP patients show increased activation for emotional words in limbic system areas in comparison with HCs.

H1.2: FEP patients show increased activation pattern for non-emotional words in limbic system areas in comparison with HCs.

2.2 Objectives

- Analysis of brain activation differences in functionally connected networks between FEP patients and HCs during passive listening to an emotional auditory paradigm.

- Analysis of brain activation differences between FEP patients and HCs to explore the potentiality of fMRI auditory emotional paradigm as an imaging biomarker.

CHAPTER II: METHODOLOGY AND DATA ANALYSIS

3. MATERIALS AND METHODS

3.1 Scope of the study

This study has been carried out within the Program of the First Episodes Psychotic Unit that is carried out in the psychiatric service belongs to area 5 of the University Clinical Hospital, in Valencia. The objectives of the program of the FEP unit are both assistance and research. From an assistance point of view, the objective is to give intensive and multidisciplinary assistance to all people in Valencia who present a first episode of psychosis.

3.2 Subject recruitment and assessment.

All patients and control participants gave written informed consent to participate in the research, which was approved by the local ethics committee (see in Annex II: Medical ethics committee). All subjects or their legal guardians provided written informed consent after study procedures were fully explained. FEP patients were recruited from Clinical University Hospital, Valencia, Spain. Patients were included in the study if they were: a) aged 15–50; b) presence of symptoms positive with or without negative / disorganized for a psychotic disorder within the first 18 months after symptom onset to (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes F20-F33; c) speak fluent Spanish; d) informed consent for the study signed by the patient. The exclusion criteria were: a) individuals who had previous contact with mental health services for psychosis, b) evidence of psychotic symptoms precipitated by an organic cause, c) transient psychotic symptoms resulting from acute intoxication, d) substance abuse (except tobacco); e) carry a metal prosthesis and f) claustrophobia.

The inclusion criteria of the controls were: a) age between 15–50 years old; b) absence of psychotic symptomatology or major depression; e) no history of psychotic disorder among first-degree relatives; c) speak fluent Spanish; d) informed consent for the study signed by the participant. The exclusion criteria for the controls were the same as for the FEP patients. No individual in either group suffered from hearing loss.

The final sample conssited of 109 subjects which included 59 FEP patients with non-affective psychotic disorders (Manic episode with psychotic features, schizoaffective disorder, transient psychotic disorders, persistent delusional disorder, bipolar affective disorder with psychotic features and schizophreniform disorder) and 50 healthy controls were included in the baseline assessments. In FEP patients sample 48 participants were male (81.4%). The total consumption of cannabis in FEP group was 23 patients (39.7%). All patients were under antipsychotic treatment at the time of evaluation: 53 (91.4%) under atypical antipsychotics, and 5 (8.6%) under typical antipsychotics. Patients' educational level was as follows: Elementary= 29 (50%), secondary = 18 (31%) and university = 11 (19%). In HCs the education levels was elementary= 2 (4%), secondary = 18 (36%) and university = 30 (60%). The mean age in FEP was 28.19 years and in HCs was 31.36. The mean duration of psychosis (DUP) was 4.63 months (S.D.=2.6). The variables of interest that we are useful for the realization of this research were: Patient personal data (age and sex), socio-demographic data (place of birth, ethnicity, educational level), cannabis consumption, diagnosis, type of antipsychosis, psychiatric pathology (axis I ICD10) and psychopathological assessments.

3.3 Psychopathological assessments.

All FEP patients underwent through several psychopathological assessments which included Clinical global impression (CGI) (Haro *et al.*, 2003) to provide a global rating of illness severity, improvement and response to treatment, Global Assessment of Function (GAF) (Jones *et al.*, 1995) to provide understanding about how well FEP patients could do everyday activities and also PANSS which is a well-established scale that has been used to objectively assess for schizophrenia symptoms (Kay, A. Fiszbein, *et al.*, 1987). Each item was scored from 1 to 7, for PANSS +, PANSS − and PANSS General Psychopatology. In the analyses, we used the total PANSS sum of positive, negative and general psychopatology scores (see in Annex I: Data collection booklet at First-Episode Psychosis Unit of the Hospital Universitario Clínico of Valencia).

3.4 Experimental paradigm.

All participants were evaluated at fMRI with an emotional auditory paradigm that was designed and applied in several publications to replicate the emotional response in chronic psychotic patients (Martí-Bonmatí *et al.*, 2007; Sanjuan *et al.*, 2007; Escartí *et al.*, 2010; Aguilar *et al.*, 2018).

3.5 Selection of emotional and neutral words.

An emotional response paradigm was designed in eighty-two patients with schizophrenia meeting DSM-IV (APA, 1994) criteria with hallucinations were selected in order to choose words of emotional content specific to their psychoses. Hallucinations patients were administered the PSYRATS (Haddock *et al.*, 1999) and their discourses about the content of hallucinations were recorded on tape.

The recordings underwent transcription. Qualitative data were analyzed using the methodology proposed by Miles and Huberman (Miles MB, 1994). Hallucinations based on complex phrases or with neutral content were ruled out. A total of 65 words were chosen based on their frequency, including only those possessing meaning by themselves (Sanjuan *et al.*, 2007). Given that the stimuli pattern for the fMRI experiment lasts 20 seconds for each block, a total number of 13 words were selected according to their frequency in the recording, and then grouped as follows: four imperative words of negative content, three insults, two words with imperative tone, two exclamations related to emotions, and two words of positive content.

For the selection of neutral words (non-emotional), we used data published by Algarabel (Algarabel González, 1996) in which the rate of psychological interest of 1917 Spanish words was described. Subjective rates were obtained from a group of 2000 subjects (from Valencia and Alicante, Spain) who evaluated words on a scale from 1 to 7. The most relevant item for this study was “pleasantness”. Subjects had to answer to which degree the word triggered pleasant or unpleasant feelings, on a scale in which 1=very unpleasant and 7=very pleasant. The pleasantness average rate of neutral words was 3.8. The pleasantness average rate of emotional selected words was 1.4 for words of negative content, 1.2 for insults, 1.5 for words with imperative tone, 2.1 for exclamations related to emotions, and 5.8 for words of positive content (Sanjuan *et al.*, 2007).

Finally, the total number of syllables for the neutral words (n=33) was the same that the number of syllables in the emotional words (n=33). For the recording procedure, a professional actor from a specialized center was hired to pronounce the words. He pronounced neutral words using a neutral tone and emotional words using an emotional tone but maintaining voice intensity constant (65 dB).

3.6 Imaging acquisition.

The fMRI images were obtained by means of BOLD (Ogawa *et al.*, 1993) contrast, applying the stimulation paradigm described before. Participants were binaurally stimulated in two different sessions. Figure 9 represents the distribution of the blocks for both sessions in time. The activation blocks in the first session consisted of 13 Spanish words containing high emotional content. The second session had activation blocks containing 13 words having neutral or low emotional content.

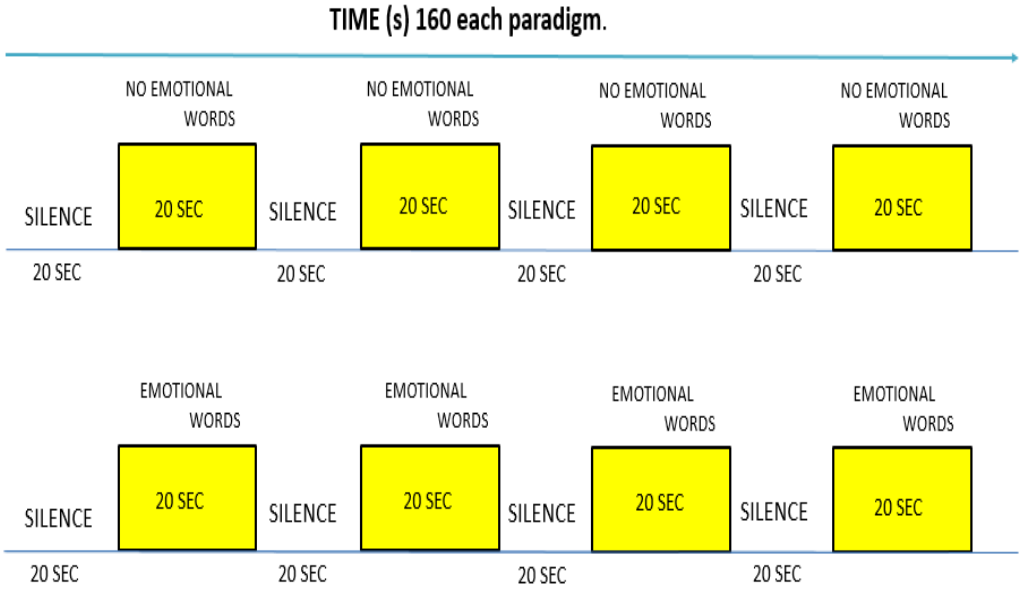

Figure 9:Neutral and emotional auditory paradigm patterns during fMRI acquisition.

Four blocks of stimuli, 20 seconds each, interleaved with another four blocks of rest of 20 seconds each, were presented to patients and controls (Figure 9). The acquisition order (no emotional and emotional words) was randomized to avoid biases (habituation, fatigue, saturation and surprise).

Subjects were informed before the test about the two types of words they were going to listen to, and were asked to focus their attention on them. Subjects were scanned with Philips 3T magnets (Achieva, Philips Medical Systems, Best, The Netherlands). Subjects used earphones connected by a pair of air tubes to an external audio player. The acquisition was performed with a 32-channel head coil.

A dynamic echo planar imaging (EPI) T2* weighted MR sequence (repetition time = 2000 msec; echo time = 30 msec; section thickness = 3·50 mm with no interslice gap; flip angle 90; matrix 128 × 128; pixel size 1·80 × 1·80 mm) was obtained, and each dynamic acquisition was composed of 40 contiguous slices covering the whole brain. The total duration of the fMR sequence was 160 s. Parametric fMR imaging maps were obtained for each participant. Anatomical labeling of the activated areas was obtained by using a normalized atlas.

During the acquisition, patients were under direct observations and asked about their experiences inmmediately after the fMRI procedure.

3.7 Data analysis.

We first estimated differences between groups in sociodemographic and clinical data we performed t-student test for variables with continuous scores and chi square for categorial using a statistical analysis software SPSS (Statistical Package for Social Sciences).

We next investigate activation maps in FEP patients and HCs. The data were processed carried out with the SPM (SPM8, Wellcome Institute, London, United Kingdom) was used to perform the image processing. The tests were carried out using MATLAB R2017a (The MathWorks, Natick, MA, USA). All images were anonymized and sent to SPM and MATLAB for analysis.

MR images were initially processed to allow voxel based stadistical analyses. Functional images were realigned to correct involuntary movement of the patient's head during the test. Subsequently, a temporary correction was applied to correct the lags between the different dynamics (slice timming). The images were normalized against a standard EPI template that allowed estimating neuronal oscillations between different individuals. Image intensity was smoothed by means of a Gaussian three-dimensional 6 –mm kernel, approaching the data to a normal distribution necessary for later stadistical test. Stadistical analysis was performed first on each individual subject and also through comparation between subjects.

3.8 Statistics

The statistical analysis was performed with one sample *t*-test with SPM8 from the final sample of 50 healthy control and 59 FEP (first level analysis), applying a random effects analysis that accounts for within- and between-subject differences, extracting common features, following the GLM over the subtraction of contrasts. Individual maps of functional activation were extracted for each subject. Then a two sample *t*-test analysis (second level) was performed with SPM8 to account for group differences of activation between FEP patients and HCs activation when auditory paradigm was applied.

Significance criteria were established by using a ($P<0.05$) and a correction for multiple comparisons following the Familywise Error Rate (FWE) methodology. In some comparisons, a threshold of ($P<0.001$) uncorrected was also considered for exploratory purposes. Then, maps of significant differences in BOLD signal in all FEP and HCs between emotional words and non-emotional words were calculated.

Areas of activation were delimited with the atlas proposed by Schmahmann et al (Schmahmann *et al.*, 1999) This atlas is included in the Automatic Area Labeling (AAL) of activations in SPM software (Tzourio-Mazoyer *et al.*, 2002). Areas-identifying coordinates were determined by the maximum Student-t value in the corresponding brain area, which extract a table with all local maxima of activation and the areas they correspond to in the labelled atlas.

CHAPTER III: RESULTS OF THE STUDY

4. RESULTS

4.1 Sociodemographic and Psychopathological data.

There were significant differences in age (F=6.16, P< .015) and sex (χ^2 = 18.04, P< .001) between groups. Across FEP patients and HCs groups we also found significant differences in education level (χ^2 = 32.39, P< .001) and cannabis consumption (χ^2 = 25.19, P< .001). However, these groups did not differ in ethnicity (χ^2 = 2.61, P< .027). Demographic characteristics of the FEP and HCs groups are summarised in Table 6.

Table 6:Full Demographic and clinical characteristics of the FEP and HCs.

	FEP N= 59	**Healthy Controls N= 50**	**F/ χ^2**	**p value**
Age in years: mean (SD)	28.19 (8.84)	31.36 (6.52)	F = 6.16	P<0.015
Sex: no. (%)			χ^2 = 18.04	P<0.001
Male	48 (81.4%)	21 (42.0%)		
Female	11 (18.6%)	29 (58.0%)		
Ethnicity: no. (%)			χ^2 = 2.61	P<0.271
Caucasian	56 (94.9%)	50 (100%)		
Other	3 (5.1%)	-		
Educational level			χ^2 = 32.39	P<0.001
Elementary	29 (50.0%)	2 (4.0%)	-	-
Secondary	18 (31.0%)	18 (36.0%)	-	-
University	11 (19.0%)	30 (60.0%)	-	-
Cannabis consumption			χ^2 = 25.19	P<0.001
Yes	23 (39.7%)	-	-	-
No	35 (60.3%)	50 (100%)	-	-
Diagnosis				
Manic episode with psychotic features (F30.0)	1 (1.7%)	-	-	-
Schizoaffective disorder (F25.0)	4 (6.8%)	-	-	-
Transient psychotic disorders (F23.0)	1 (1.7%)	-	-	-
Persistent delusional disorder (F22.0)	3 (5.1%)	-	-	-
Bipolar affective disorder with psychotic features (F31.0)	1 (1.7%)	-	-	-
Schizophreniform disorder (F20.8)	49 (83.1%)	-	-	-
Treatment (Type of antipsychosis)				
Typical antipsychotics	5 (8.5%)	-	-	-
Atypical antipsychotics	53 (91.5%)	-	-	-

Table 7 displays significant differences within age level groups. FEP patients were much younger than the control group. The mean age of the patients was 28.19 years old, and the mean age of the controls was 31.36 years.

Table 7:Differences in age between groups.

	GROUP	N	Mean	Standard Deviation.	Typical Error
AGE	FEP	59	28,19	8,842	1,151
	CONTROL	50	31,36	6,527	,923

		Levene's test for equality of variances		T test					
		F	Sig.	t	df	Sig. (bilateral)	Mean difference	95% Confidence interval for the difference	
								Inferior	Superior
AGE	Equal varianes	6,168	,015	-2,099	107	,038	-3,174	-6,171	-,176
	Unequal variances			-2,151	105,121	,034	-3,174	-6,099	-,248

In the FEP group, males comprised of more than half of the study population which encompassed 81%. However, in the HCs group the male sample was clearly compased by 42% (see table 8). Given this difference in sex, we used this variable as covariate to explore effects that interaced with the emotional auditory paradigm in the fMRI vowel-wise analyses.

Table 8:Chi square sex between groups.

			GROUP		Total
			CONTROL	FEP	
SEX	FEMALE	Count values cases	29	11	40
		% within GROUP count cases	58,0%	18,6%	36,7%
	MALE	Count values cases	21	48	69
		% within GROUP count cases	42,0%	81,4%	63,3%
Total		Count values cases	50	59	109
		% within GROUP count cases	100,0%	100,0%	100,0%

	Value	df	Sig asymptotic (bilateral)	Exact Sig (bilateral)	Exact sig (unilateral)
Pearson's Chi-square	18,045	1	,000		
Correction for continuity	16,391	1	,000		
Likelihood ratio	18,507	1	,000		
Fisher's exact statistic				,000	,000
N of valid cases	109				

Ethnicity did not differ between FEP group and HCs (p< .271) (Table 9).

Table 9:Chi square ethnicity between groups.

			GROUP		Total
			CONTROL	FEP	
ETNICITY	CAUCASICAN	Count values cases	50	56	106
		% within GROUP count cases	100,0%	94,9%	97,2%
	CARIBBEAN	Count values cases	0	1	1
		% within GROUP count cases	0,0%	1,7%	0,9%
	HISPANIC	Count values cases	0	2	2
		% within GROUP count cases	0,0%	3,4%	1,8%
Total		Count values cases	50	59	109
		% within GROUP count cases	100,0%	100,0%	100,0%

	Value	df	Sig asymptotic (bilateral)
Pearson's Chi-square	2,614	2	,271
Likelihood ratio	3,755	2	,153
N of valid cases	109		

Education level (Table 10) undoubtedly showed distinction between FEP patients as compared with HCs. Patients had lower educational achievement than HCs.

Table 10:Chi square education between groups.

			GROUP		Total
			CONTROL	FEP	
EDUCATION LEVEL	PRIMARY	Count values cases	0	15	15
		% within GROUP count cases	0,0%	25,9%	13,9%
	SECUNDARY UNTIL 16YRS OLD	Count values cases	2	14	16
		% within GROUP count cases	4,0%	24,1%	14,8%
	SECUNDARY UNTIL 18YRS OLD	Count values cases	18	18	36
		% within GROUP count cases	36,0%	31,0%	33,3%
	UNIVERSITY	Count values cases	31	11	42
		% within GROUP count cases	60,0%	19,0%	38,0%
Total		Count values cases	51	58	109
		% within GROUP count cases	100,0%	100,0%	100,0%

	Valor	gl	Sig. asintótica (bilateral)
Pearson's Chi-square	32,390	3	,000
Likelihood ratio	39,476	3	,000
N of valid cases	108		

There was a compelling main effect in cannabis use (Table 11) among the FEP group as compared with the HCs.

Table 11:Chi square cannabis use between groups.

			GROUP		Total
			CONTROL	FEP	
CANNABIS CONSUMPTION	NO	Count values cases	50	35	85
		% within GROUP count cases	100,0%	60,3%	78,7%
	SI	Count values cases	0	23	23
		% within GROUP count cases	0,0%	39,7%	21,3%
Total		Count values cases	50	58	108
		% within GROUP count cases	100,0%	100,0%	100,0%

	Value	df	Sig asymptotic (bilateral)	Exact Sig (bilateral)	Exact sig (unilateral)
Pearson's Chi-square	25,193	1	,000		
Correction for continuity	22,882	1	,000		
Likelihood ratio	33,953	1	,000		
Fisher's exact statistic				,000	,000
N of valid cases	108				

There were also indicative differences in antipsychotic treatment within the FEP group (Table 12). Although, the atypical antipsychotic medication was mostly used in patients.

Table 12: Antipsychotic treatment within FEP.

			GROUP FEP
ANTIPSYCHOTIC TREATMENT	ATYPIC ANTIPSYCHOTIC	Count values cases	54
		% within GROUP count cases	91,5%
	TYPICAL ANTIPSYCHOTIC	Count values cases	5
		% within GROUP count cases	8,5%
Total		Count values cases	59
		% within GROUP count cases	100,0%

Diagnoses were made according to the ICD-10 criteria. The main diagnosis was Schizophreniform disorder (F20.8) due to the vast majority of FEP patients that were within a one-month period, but signs of disruption were not present shown for the full six months required for the diagnosis of schizophrenia. Although, five other diagnoses were presently displayed, within patients as a result of the heterogeneity in early phases of psychosis (Table 13).

Table 13:Psychopathology ICD-10 criteria.

			GROUP FEP
CIE-10 PSYCHIATRIC PATHOLOGY	F22	Count values cases	3
		% within GROUP count cases	5,1%
	F23	Count values cases	1
		% within GROUP count cases	1,7%
	F25	Count values cases	4
		% within GROUP count cases	6,8%
	F20.8	Count values cases	49
		% within GROUP count cases	83,1%
	F30	Count values cases	1
		% within GROUP count cases	1,7%
	F31	Count values cases	1
		% within GROUP count cases	1,7%
Total		Count values cases	59
		% within GROUP count cases	100,0%

4.2 Psychopathological assessments.

Regarding psychopathological data, (Table 14) shows summary of included psychopatological assessments. FEP patients were clinically assessed with CGI (Table 15) mean score was 4.10 (S.D 0.80) presenting overt symptoms causing noticeable, but modest, functional impairment or distress.

Table 14:Summary of distribution characteristics PANSS, CGI and GAF.

Distribution characteristics	Positive	Negative	General Psychopathology	Total PANSS	CGI	GAF
Mean	16.61	16.00	34.32	67.05	4.10	58.28
Median	14.00	15.00	33.00	70.00	4	60
Standar Deviation	5.66	5.26	9.2	17.36	0.80	13.48

Table 15:Satatics CGI scale

GROUP FEP			Statistical	Typical Error
GENERAL CLINICAL IMPRESSION SCALE	Mean		4,10	,105
	95% confidence interval	Lower limit	3,89	
		Upper limit	4,31	
	Median		4,00	
	Variance		,645	
	Mínimum		3	
	Maximum		6	
	Rank		3	
	Asymmetry		,018	,311
	Kurtosis		-,978	,613

In reference to GAF scale (Table 16), the mean score was 58.28 (SD 13.48) showing moderate difficulties in social, occupational, or school functioning activities. Conflicts with peers, co-workers and having a few friends were also displayed.

Table 16:Statics GAF scale.

GROUP FEP			Statistical	Typical Error
GLOBAL ASSESSMENT OF FUNCTIONING SCALE	Mean		58,28	1,770
	95% confidence interval	Lower limit	54,73	
		Upper limit	61,82	
	Median		60,00	
	Variance		181,78	
	Mínimum		20	
	Maximum		85	
	Rank		65	
	Asymmetry		-,388	,314
	Kurtosis		,499	,618

With regard to the total PANSS, the mean score was 67.05 (SD 17.36), in the positive symptoms scale (Table 17) the mean score was 16.61 (SD 5.66), negative symptoms scale (Table 18) was 16.00 (SD 5.26), general psychopathology symptoms scale (Table 19) mean score was 34.32 (SD 9.27) and total PANSS score (Table 20) the mean was 67.05 (SD 17.36).

Table 17:Statistics PANSS positive symptoms.

GROUP FEP			Statistical	Typical Error
SUBTOTAL PANSS POSITIVA	Mean		16.61	,737
	95% confidence interval	Lower limit	15,14	
		Upper limit	18,09	
	Median		14,00	
	Variance		32,03	
	Mínimum		0	
	Maximum		30	
	Rank		30	
	Asymmetry		,386	,311
	Kurtosis		,474	,613

Table 18:Statistics PANSS negative symptoms

GROUP FEP			Statistical	Typical Error
SUBTOTAL PANSS POSITIVA	Mean		16,00	,685
	95% confidence interval	Lower limit	14,63	
		Upper limit	17,37	
	Median		15,00	
	Variance		27,72	
	Mínimum		0	
	Maximum		33	
	Rank		33	
	Asymmetry		,844	,311
	Kurtosis		3,119	,613

Table 19:Statistics PANSS General Psychopathology.

GROUP FEP			Statistical	Typical Error
SUBTOTAL PANSS POSITIVA	Mean		34,32	1,208
	95% confidence interval	Lower limit	31,90	
		Upper limit	36,74	
	Median		33,00	
	Variance		86,050	
	Mínimum		0	
	Maximum		66	
	Rank		66	
	Asymmetry		-,089	,311
	Kurtosis		3,914	,613

Table 20:Statistics PANSS total score.

GROUP FEP			Statistical	Typical Error
SUBTOTAL PANSS POSITIVA	Mean		67,05	2,260
	95% confidence interval	Lower limit	62,53	
		Upper limit	71,58	
	Median		70,00	
	Variance		301,39	
	Mínimum		0	
	Maximum		120	
	Rank		120	
	Asymmetry		-,282	,311
	Kurtosis		4,006	,613

4.3 Functional Magnetic Resonance Imaging results

4.3.1 Effect of FEP group for emotional words.

In FEP group (59 patients), SPM analysis revealed that several cortical regions displayed significant activated voxels for emotional words task after (*P*<0.05 FWE corrected). These areas included the following: left superior temporal gyrus (BA 21), right middel temporal gyrus (BA 21), right supplementary motor area (BA 06), right precentral gyrus (BA 06), bilaterally amygdala (BA 28,36), bilaterally hippocampus (BA 34) and left superior frontal gyrus medial (BA 10) in Figure 10 and Table 21.

Table 21:Increased activation with emotional words, BOLD signal, in FEP patients.

FEP_emo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
14.17	[-54 -6 -10]	Temporal_Sup_L	Bro_21
12.96	[62 -4 -12]	Temporal_Mid_R	Bro_21
8.87	[-28 -11 -18]	Hippocampus_L	Bro_35
7.30	[26 -11 -18]	Hippocampus_R	Bro_35
6.12	[24 -1 -20]	Amygdala_R	Bro_34
5.86	[-26 0 -20]	Amygdala_L	Bro_34
7.50	[4 16 60]	Supp_Motor_Area_R	Bro_06
6.62	[46 4 54]	Precentral_R	Bro_06
6.35	[-6 60 28]	Frontal_Sup_Medial_L	Bro_10

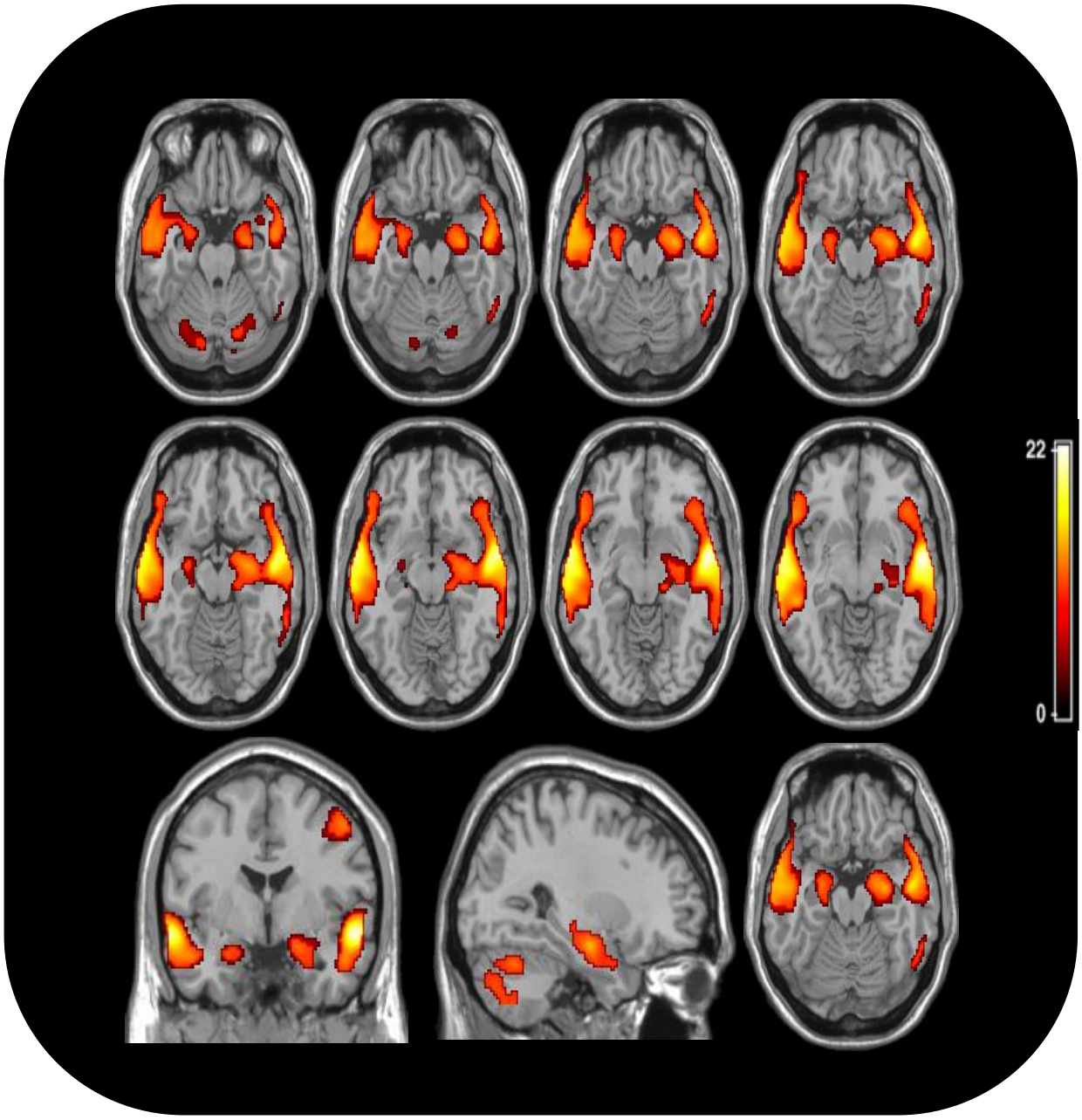

Figure 10: Regions of enhanced activaty in FEP patients under emotional auditory paradigm reported by fMRI analysis. *P*<0.05 FWE corrected *k*= 28.

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4.3.2 Effects of FEP group for non-emotional words.

During the non-emotional words task performance in FEP group, the main brain activity remained at a significat *P* value (*P*<0.05 FWE corrected). These areas comprised of the left middle temporal gyrus (BA 21), right supplementary motor area (BA 08), left parahippocampal (BA 35) and right inferior pariental (BA 40) (Figures 11 and Table 22).

Table 22:Increased activation with non-emotional words, BOLD signal, in FEP patients.

FEP_noemo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluste**	**Brodmann´s area**
15.60	[-64 -20 -4]	Temporal_Mid_L	Bro_21
9.86	[4 14 56]	Supp_Motor_Area_R	Bro_08
7.20	[-18 -12 -22]	ParaHippocampal_L	Bro_35
6.89	[52 -40 52]	Parietal_Inf_R	Bro_40

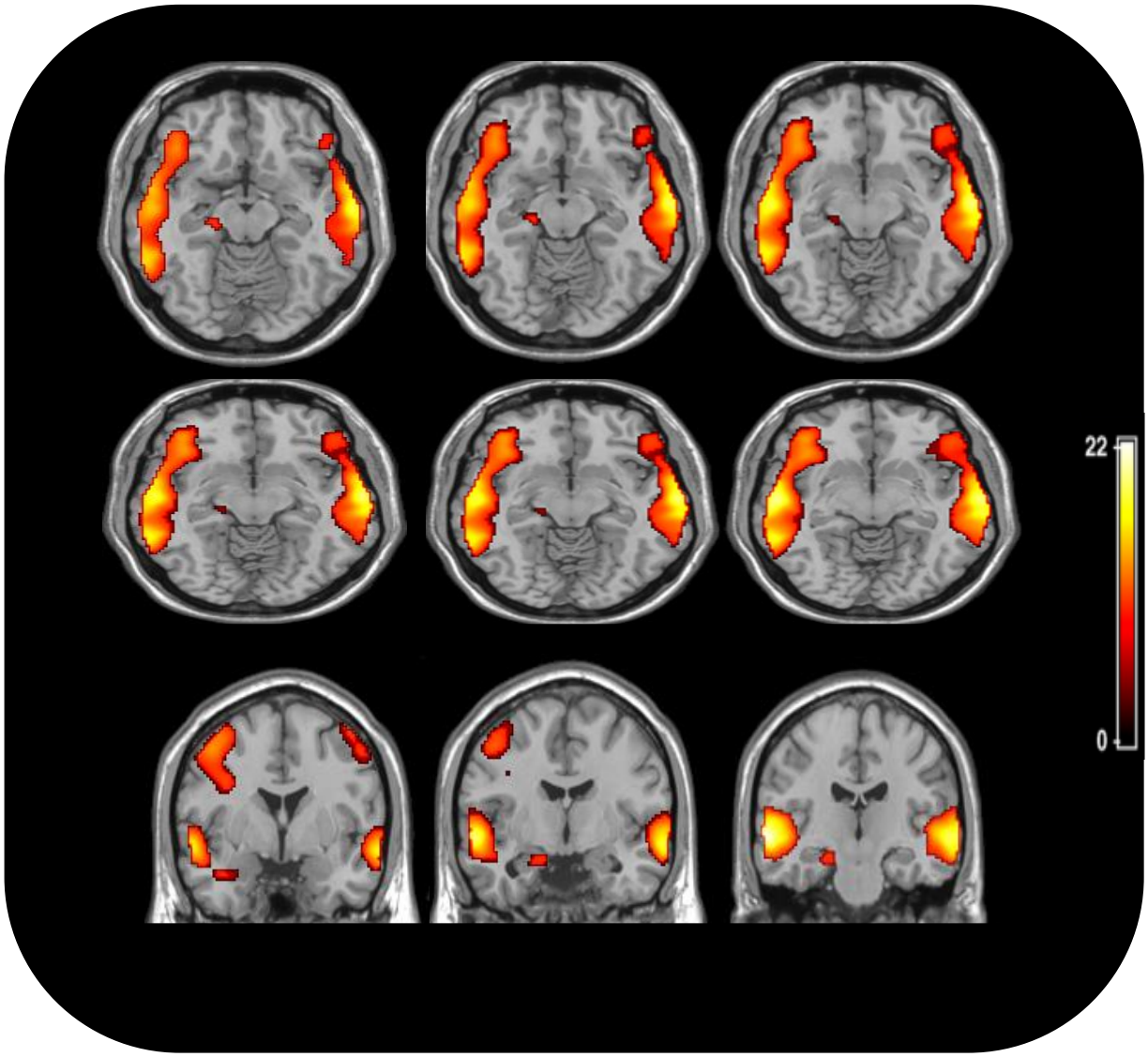

Figure 11: Regions of enhanced activaty in FEP patients under non-emotional auditory paradigm reported by fMRI analysis. *P*<0.05 FWE corrected *k*= 18.

4.3.3 Effects of FEP group between emotional and non-emotinoal words (emotional > non-emotional).

A voxel-wise whole-brain analysis of the emotional vs non-emotional words in FEP patients group revealed a clear increase of activity in the right hippocampus (BA 36) when FEP patients heard emotional words. Also, the middle right temporal gyrus (BA 20) with the considered statistical criterion ($p<0.05$ FWE-corrected) revealed greater activation during the emotional paradigm (Figure 12 and Table 23).

Table 23:FEP patients differences between areas of activation with emotional vs non-emotional words.

FEP_emo_vs_noemo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
5.03	[24 -8 -20]	Hippocampus_R	Bro_36
4.73	[50 -10 -22]	Temporal_Mid_R	Bro_20

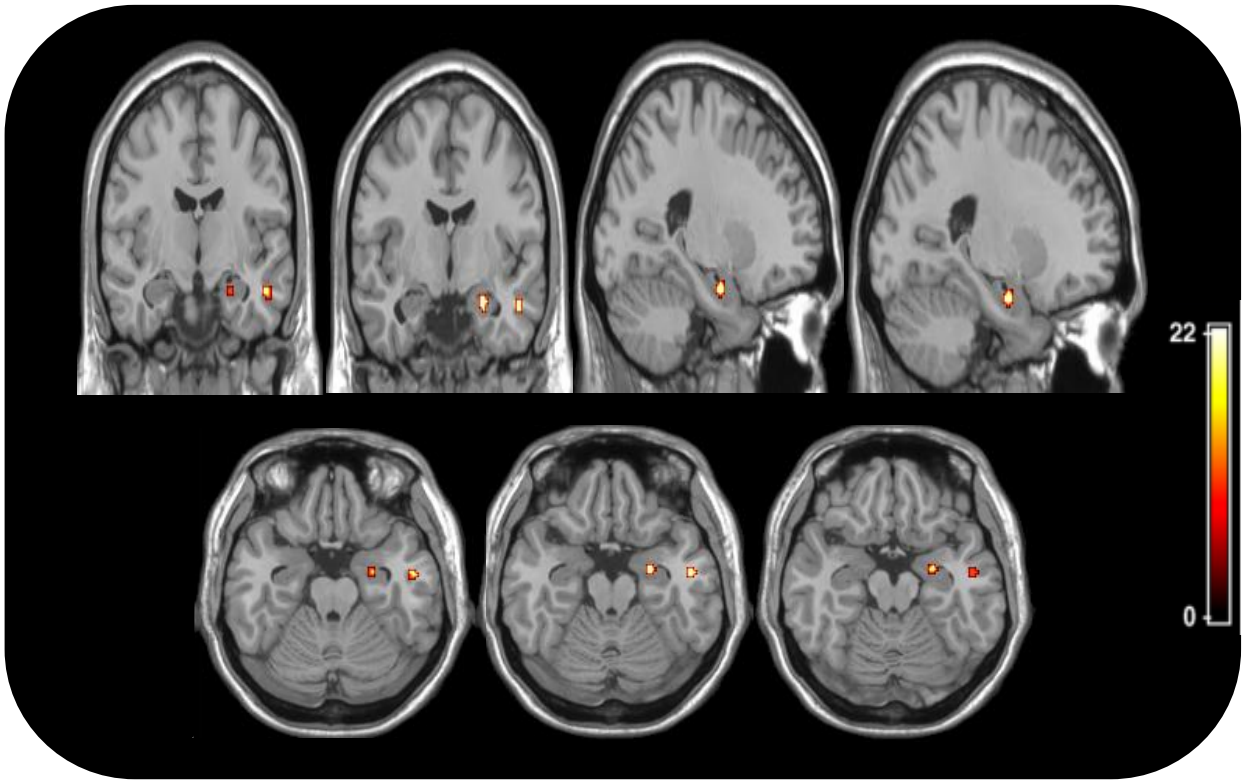

Figure 12:Activation maps between emotional vs non-emotional words show clear increase of activity in the right hippocampus and the middle right temporal gyrus in FEP patients (after *P*< 0.05 FWE corrected *k*=36).

4.3.4 Effects of HCs group for emotional words.

For the HCs group comprised of (50 participants), activation maps exposed remarkable differences between the emotional and non-emotional words task performance. Controls in the emotional words task observed that after the *P* value (*P*<0.05 FWE corrected) greater activity in bilaterally middle temporal gyrus (BA 21), supplementary motor area (BA 06), left superior frontal medial (BA 10) and bilaterally precentral gyrus (BA 06).

However, we did not find any significant increase activation of the amygdala and hippocampus when emotional words were applied in the HCs group. (Figure 13 and Tables 24).

Table 24:Increased activation with emotional words, BOLD signal, in Healthy Controls.

HC_emo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
16.10	[-62 -26 -4]	Temporal_Mid_L	Bro_21
13.63	[68 -26 -6]	Temporal_Mid_R	Bro_21
8.08	[-48 2 52]	Precentral_L	Bro_06
7.54	[6 14 62]	Supp_Motor_Area_R	Bro_06
7.33	[-6 56 28]	Frontal_Sup_Medial_L	Bro_10
7.09	[50 4 52]	Precentral_R	Bro_06
6.44	[-18 -26 -10]	Hippocampus_L	Bro_30
4.38	[8 -84 10]	Calcarine_R	Bro_17

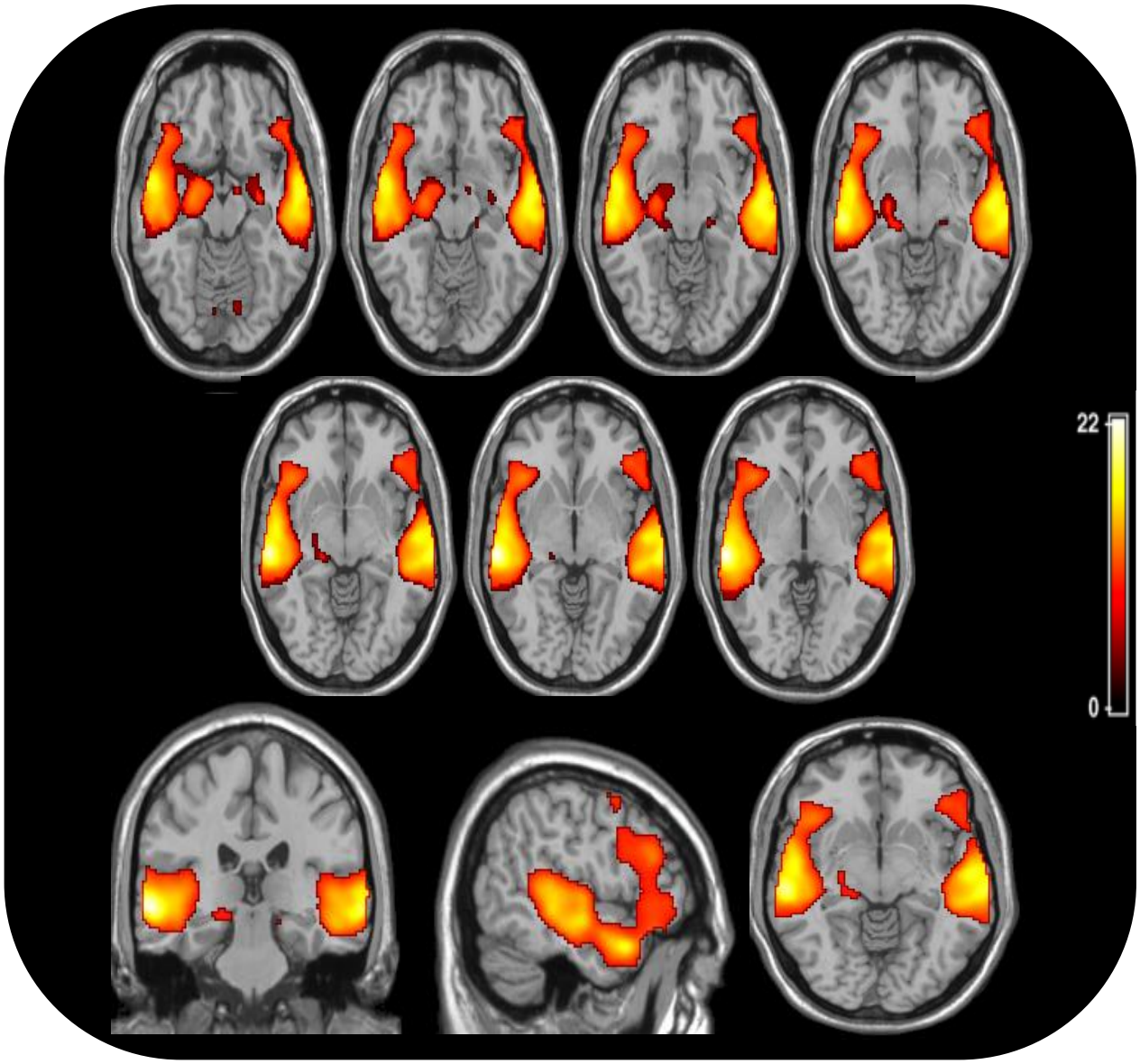

Figure 13: Regions of enhanced activaty in HCs under emotional auditory paradigm reported by fMRI analysis. *P*<0.05 FWE corrected *k*= 17.

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4.3.5 Effects of HCs group for non-emotional words.

In contrast, when non-emotional words were presented activation maps after application of a *P* value (*P*<0.05 FWE corrected) in order to see activation trends, prominent areas involved were left superior temporal gyrus (BA 22), right middle temporal gyrus (BA 21), left inferior frontal gyrus at the orbital part (BA 47) in (Figure 15,16 and Table 25).

Table 25:Increased activation with non-emotional words, BOLD signal, in Healthy Controls.

HC_noemo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
11.14	[-66 -24 0]	Temporal_Sup_L	Bro_22
10.82	[70 -28 2]	Temporal_Mid_R	Bro_21
7.13	[-42 28 -4]	Frontal_Inf_Orb_L	Bro_47

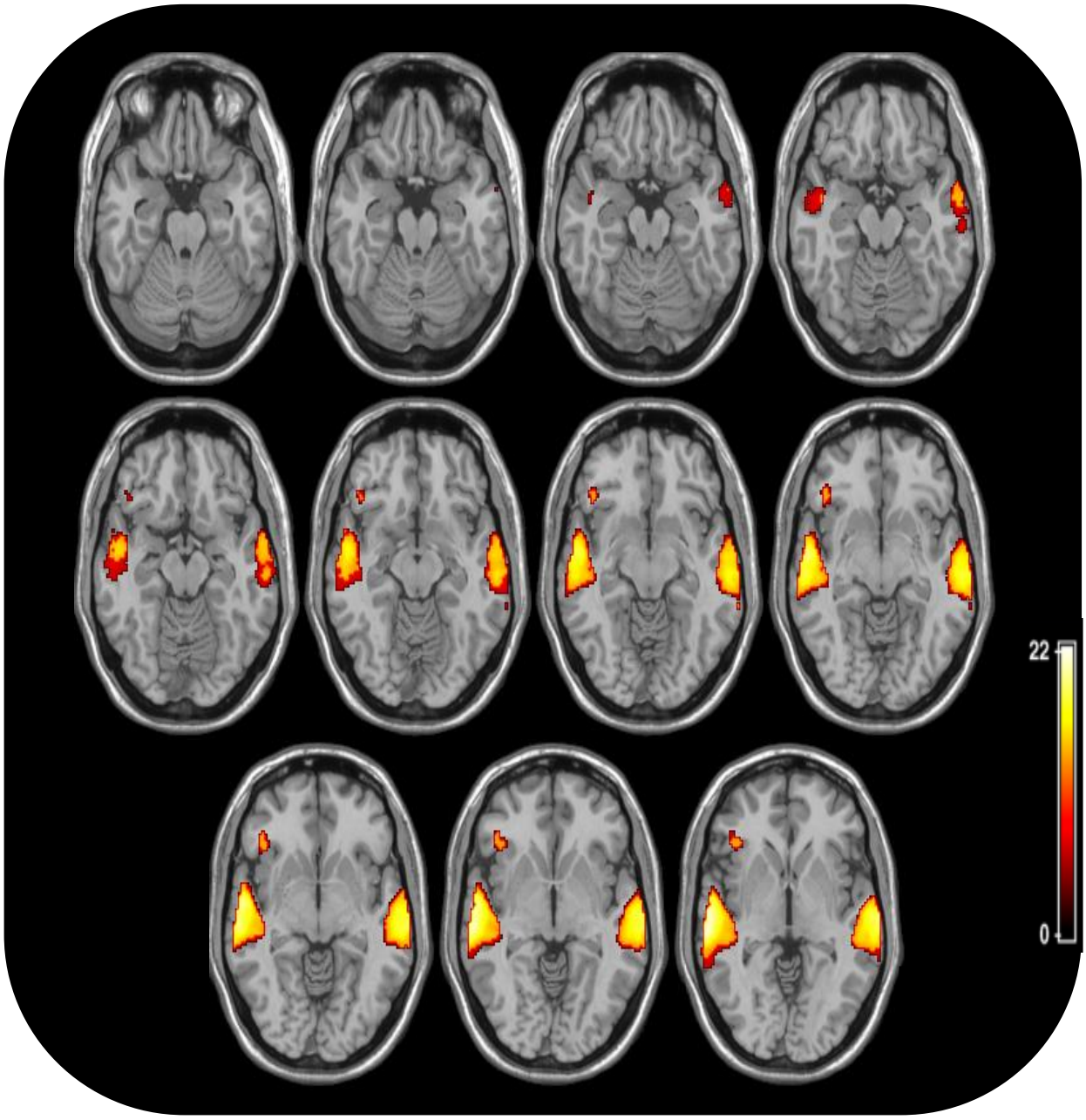

Figure 14: Highlighted areas indicate increased activation associated with non-emotional stimuli described in table 25. *P*<0.05 FWE corrected *k*=12.

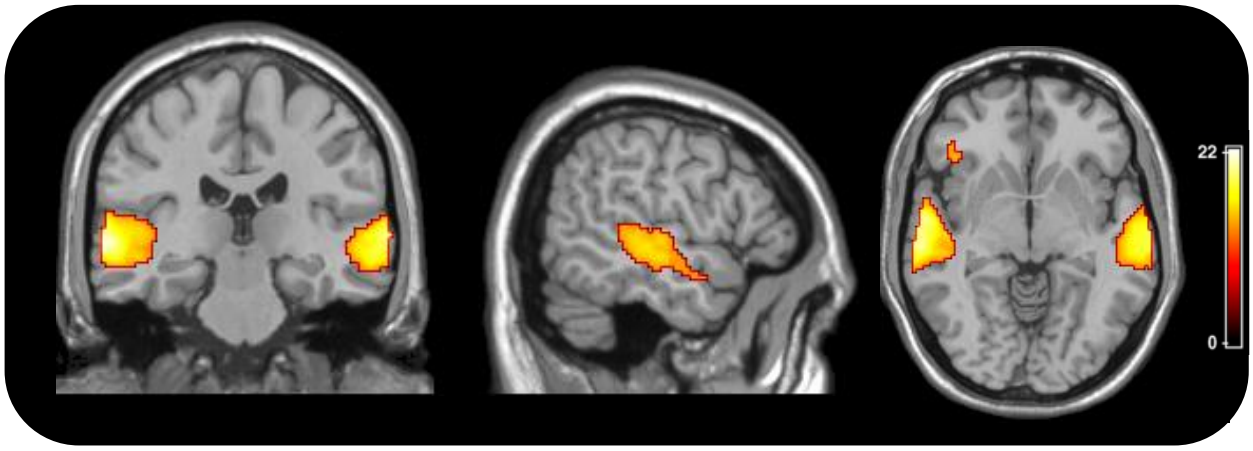

Figure 15: Main activation clusters (*P*<0.05 FWE corrected *k*=12) for non-emotional stimuli condition in superior and middle temporal lobe and left inferior frontal gyrus at the orbital part.

4.3.6 Effects of HCs group between emotional and non-emotinoal words (emotional > non-emotional).

For healthy controls, comparing activation between the two paradigms revealed significantly greater activation (*P*<0.05 FWE corrected) in bilaterally middle temporal gyrus (BA 21). We did not observe any increased activation in the hippocampal area, which appeared in the FEP patients' groups in (Figure 17 and Table 26).

Table 26:Increased activation with emotional vs non-emotional words in Healthy Controls.

HC_emo_vs_noemo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
5.59	[56 8 -24]	Temporal_Mid_R	Bro_21
5.08	[-56 -54 10]	Temporal_Mid_L	Bro_21

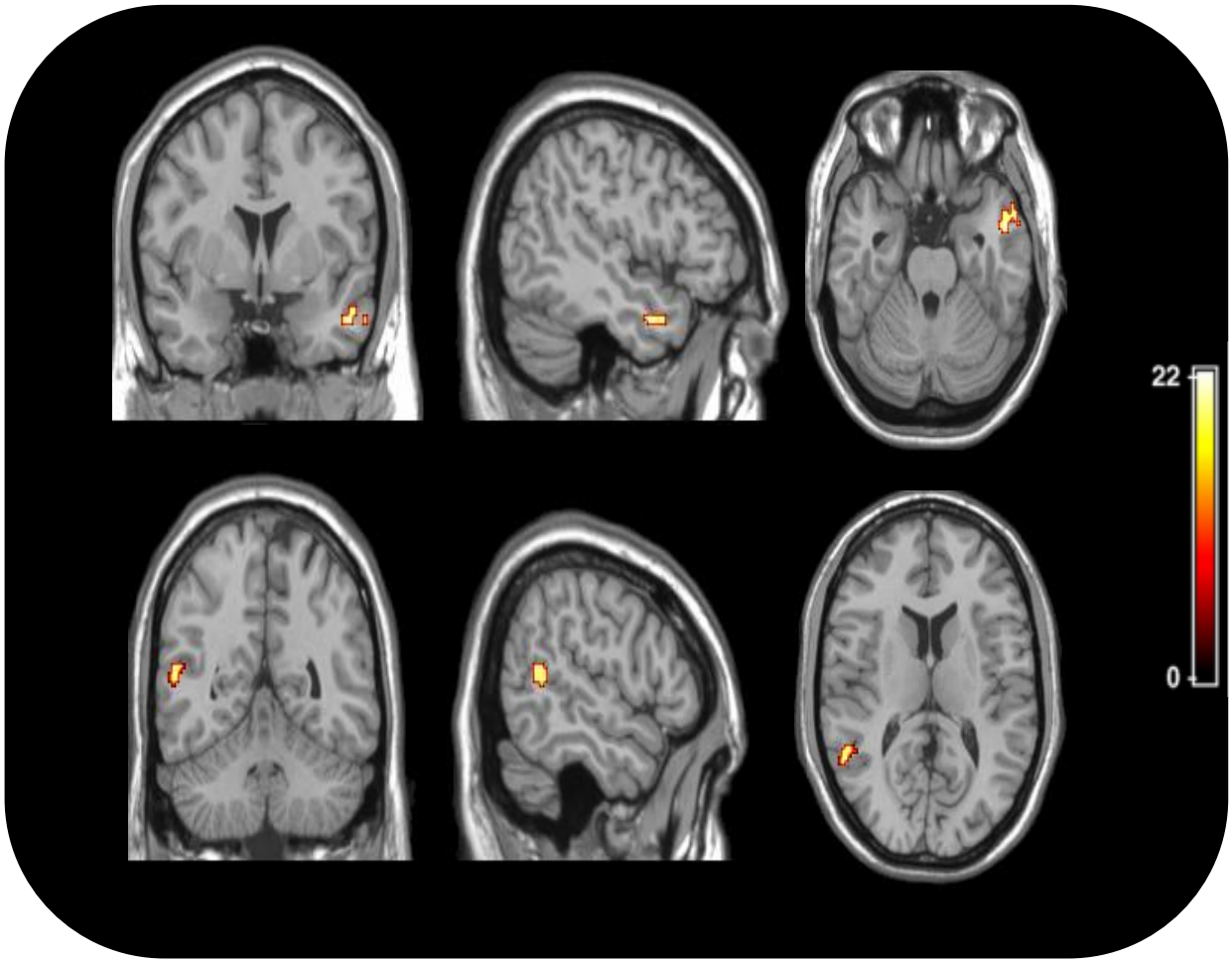

Figure 16:Activation maps between emotional vs non-emotional words show clear increase of activity in middle left and right temporal gyrus in HCs subjects (after $P< 0.05$ FWE corrected $k= 22$).

4.3.7 fMRI differences between-Group Analyses (emotional > non-emotional).

When comparing FEP and HCs groups, activation map did not show any activation with the threshold applied (*P*<0.05 FWE corrected) when emotional and non-emotional words were presented. After an application of a less rigorous *P* value (*P*<0.001 uncorrected) results did not show differences between emotional and non-emotional paradigms (See Annex III: Activation maps SPM/Contrast_FEP_vs_HCs).

4.3.8 PANSS score regression with fMRI.

A significant statistical correlation was found for the relationship between the positive subscale PANSS score and frontal lobe activity. The correlation was positive; the higher the score on the positive subscale PANSS, the higher the activation in left frontal inferior orbital (Figure 18 and Table 27). Additional positive correlation included the right temporal medial gyrus was found in the negative subscale PANSS score (Figure 19 and Table 28). No results were found for: general psychopatology subscale PANSS score and total PANSS score. There were also not regions showing a negative correlation.

Table 27:Areas with a positive correlation between the positive subscale PANSS and brain activation in FEP patients.

Positive_Correlation_PANSS_POSITIVE_FEP_emo_group P>0.001 uncc				
T_Student	**Coordenada_del_Max**	**Valor_etiqueta_segun_ATLAS**	**Brodman n**	**Pearson coefficients**
3.91	[-54 26 22]	Frontal_Inf_Orb_L	Bro_47	0.45

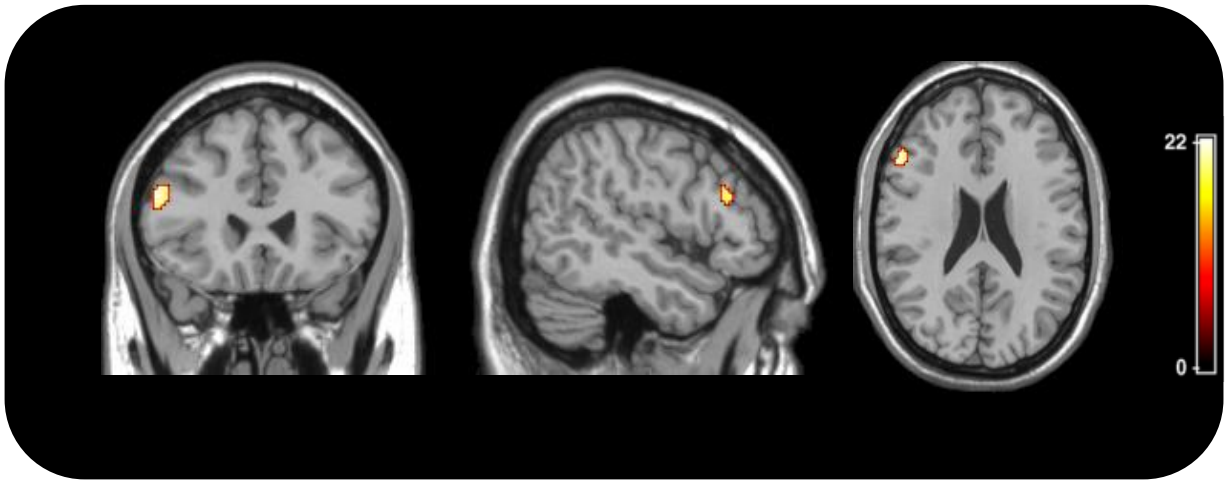

Figure 17: fMRI activation maps in FEP patients show increased in left frontal inferior orbital activation (the greater the positive PANSS score, the greater the activity). Thus, for illustrational purposes, a *P*<0.001 uncorrected *k*= 90.

Table 28:Areas with a positive correlation between the negative subscale PANSS and brain activation in FEP patients.

Positive_Correlation_PANSS_NEGATIVE_FEP_emo_group P>0.001 uncc				
T_Student	**Coordenada_del_Max**	**Valor_etiqueta_segun_ATLAS**	**Brodmann**	**Pearson coefficients**
3.41	[54 44 4]	Temporal_Mid_R	Bro_21	0.41

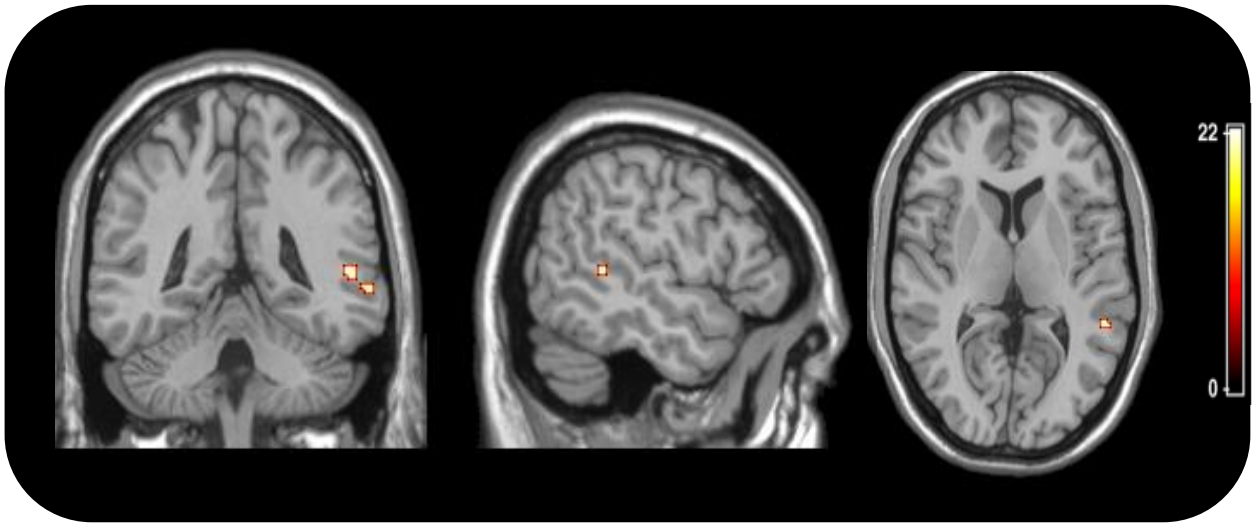

Figure 18: fMRI activation maps in FEP patients show increased in right middle temporal gyrus activation (the greater the positive PANSS score, the greater the activity). Thus, for illustrational purposes, a *P*<0.001 uncorrected *k*= 91.

In total, these findings provide evidence that the limbic system activity during auditory paradigm differs clearly between emotional and non-emotional words. FEP patients mostly showed increased activation in hippocampal areas, in both conditions (emotional and non-emotional). Furthermore, amygdala appears to be affected only during emotional paradigm in FEP patients.

Activation maps in HCs also display differences between emotional and non-emotional paradigm. HCs subjects showed activation in left hippocampus only when high emotional contect stimulis was presented. Moreover, there was also an effect during the non-emotional condition in left inferior frontal gyrus at the orbital part.

4.3.9 Sex effects observed in the fMRI.

A. FEP female patients' activation compared with HCs female.

Using AAL atlas we found significant main effect (*P*<0.001 uncorrected) sex-by-group interaction in female FEP patients compared with females HCs for emotional paradigm in bilaterally superior and middle frontal lobe (BA 8,9,46) and left anterior cingulum (BA 32) see Figure 20 and Table 29.

Table 29:Same sex-by-group interaction enhanced activation in emotional words.

Females_FEP_emo_vs_Females_HCs_emo_group P<0.001 uncorrected			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
4.39	[-16 14 54]	Frontal_Sup_L	Bro_08
4.06	[18 20 50]	Frontal_Sup_R	Bro_08
3.80	[-42 40 32]	Frontal_Mid_L	Bro_46
3.77	[-10 34 24]	Cingulate_Ant_L	Bro_32
3.69	[38 40 40]	Frontal_Mid_R	Bro_09

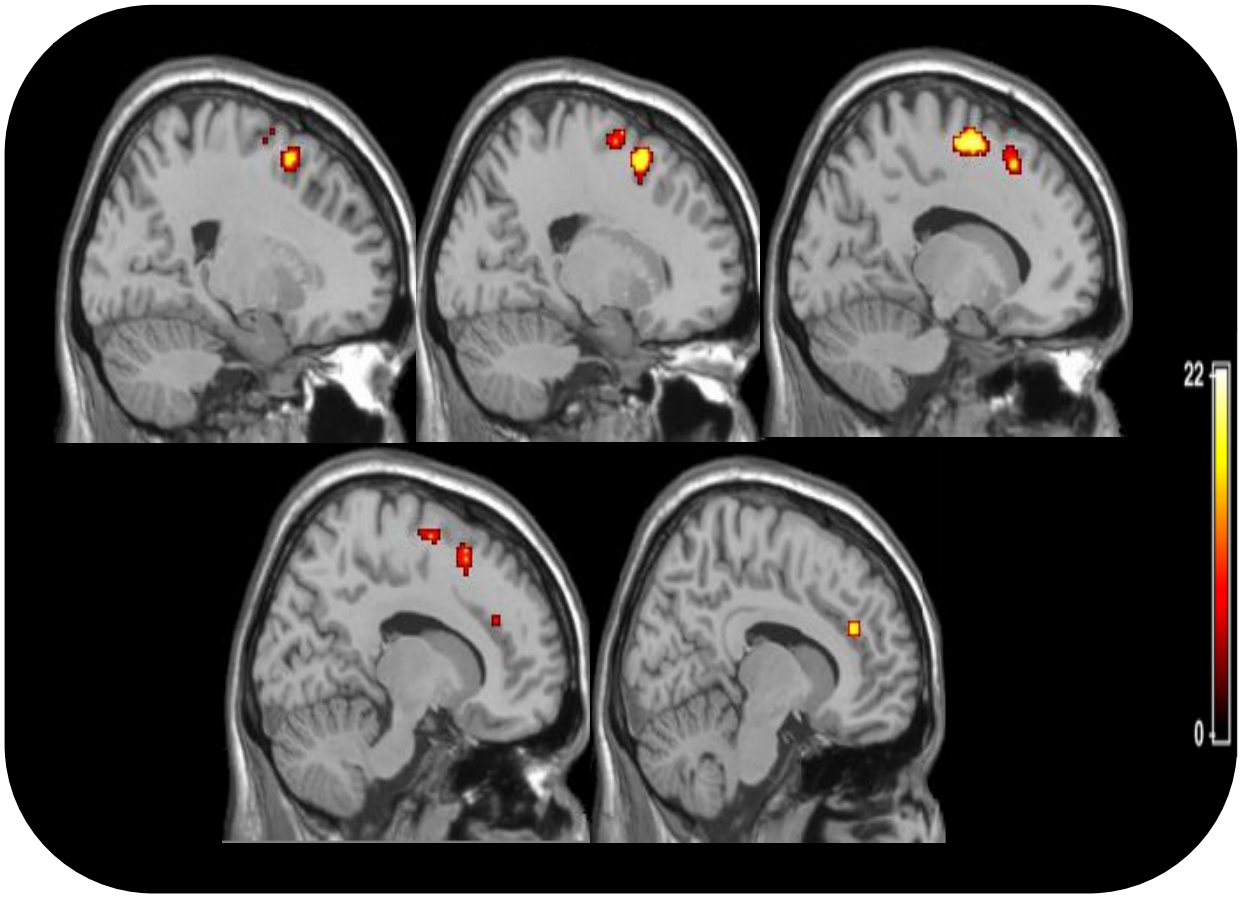

Figure 19: Activation maps in female FEP patients comparing female HCs under emotional content stimuli. Areas with fMRI response are forntal superior and left anterior cingulate. (P<0.001, uncorrected *k*= 74*).*

There were also significant effects of group females FEP patients compared with females HCs for non-emotional paradigm. Significant sex-by-interaction was observed across the right orbitofrontal cortex (BA 11), right supplementary motor area (BA 6), right precentral gyrus (BA 6), and right middle frontal lobe (BA 46) (Figure 21 and Table 30). Indicating that female FEP patients differ from female HCs showing increased activation in prefrontal areas such as right orbitofrontal cortex when non-emotional paradigm was performed.

Table 30:Same sex-by-group interaction enhanced activation in non-emotional words.

Females_FEP_nonemo_vs_Females_HCs_nonemo _group P<0.001 uncorrected			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodman n´s area**
4.08	[18 38 -2]	Orbitofrontal_cortex_ R	Bro_11
3.91	[2 20 56]	Supp_Motor_Area_R	Bro_06
3.72	[32 -14 56]	Precentral_R	Bro_06
3.69	[30 24 40]	Frontal_Mid_R	Bro_46

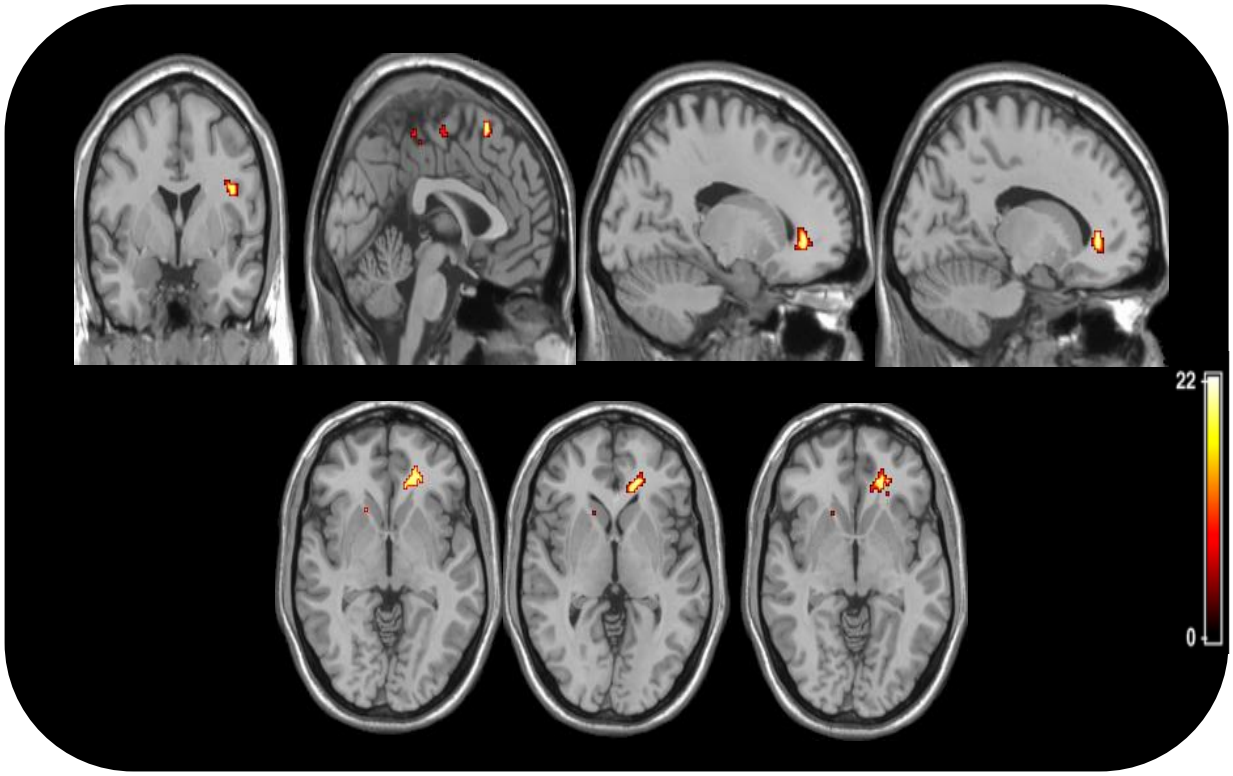

Figure 20: Activation maps in female FEP patients comparing female HCs under non-emotional content stimuli. Areas with fMRI response are mainly right orbitofrontal cortex, right precentral gyrus and right middle frontal. (*P*<0.001, uncorrected *k*= 45).

B. FEP male patients' activation compared with HCs male.

The functional MRI results for male FEP patients compared with male HCs during emotional paradigm do not survivie neither FEW correction (*P*<0.05) nor with less rigorous *P* value (*P*<0.001 uncorrected) (See Annex III: Activation maps SPM/FEPmale_vs_HCmale_emo). Whereas male FEP patients in non-emotional paradigm showed a fairly significant effect with the threshold applied (*P*<0.001 uncorrected). As shown in Figure 22 and Table 31, increased activation in male FEP patients.

Table 31:Areas of activation in same sex-by-group interaction with non-emotional words.

Males_FEP_nonemo_vs_Males_HCs_nonemo_group P<0.001 uncorrected			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
4.59	[8 -74 40]	Precuneus_R	Bro_07
4.57	[52 -56 16]	Temporal_Mid_R	Bro_21
4.13	[-34 -64 42]	Angular_L	Bro_07
3.93	[10 56 12]	Frontal_Sup_Medial_R	Bro_10
3.74	[-52 -42 56]	Parietal_Inf_L	Bro_40
3.73	[12 -48 34]	Cingulate_Post_R	Bro_31
3.68	[-54 -50 -12]	Temporal_Inf_L	Bro_20
3.65	[48 -36 -16]	Temporal_Inf_R	Bro_20
3.62	[36 60 8]	Frontal_Mid_R	Bro_10
3.56	[8 32 56]	Frontal_Sup_Medial_R	Bro_08
3.41	[-1 -34 38]	Cingulate_Mid_L	Bro_23
3.39	[62 16 18]	Frontal_Inf_Oper_R	Bro_44
3.36	[-26 28 40]	Frontal_Mid_L	Bro_09

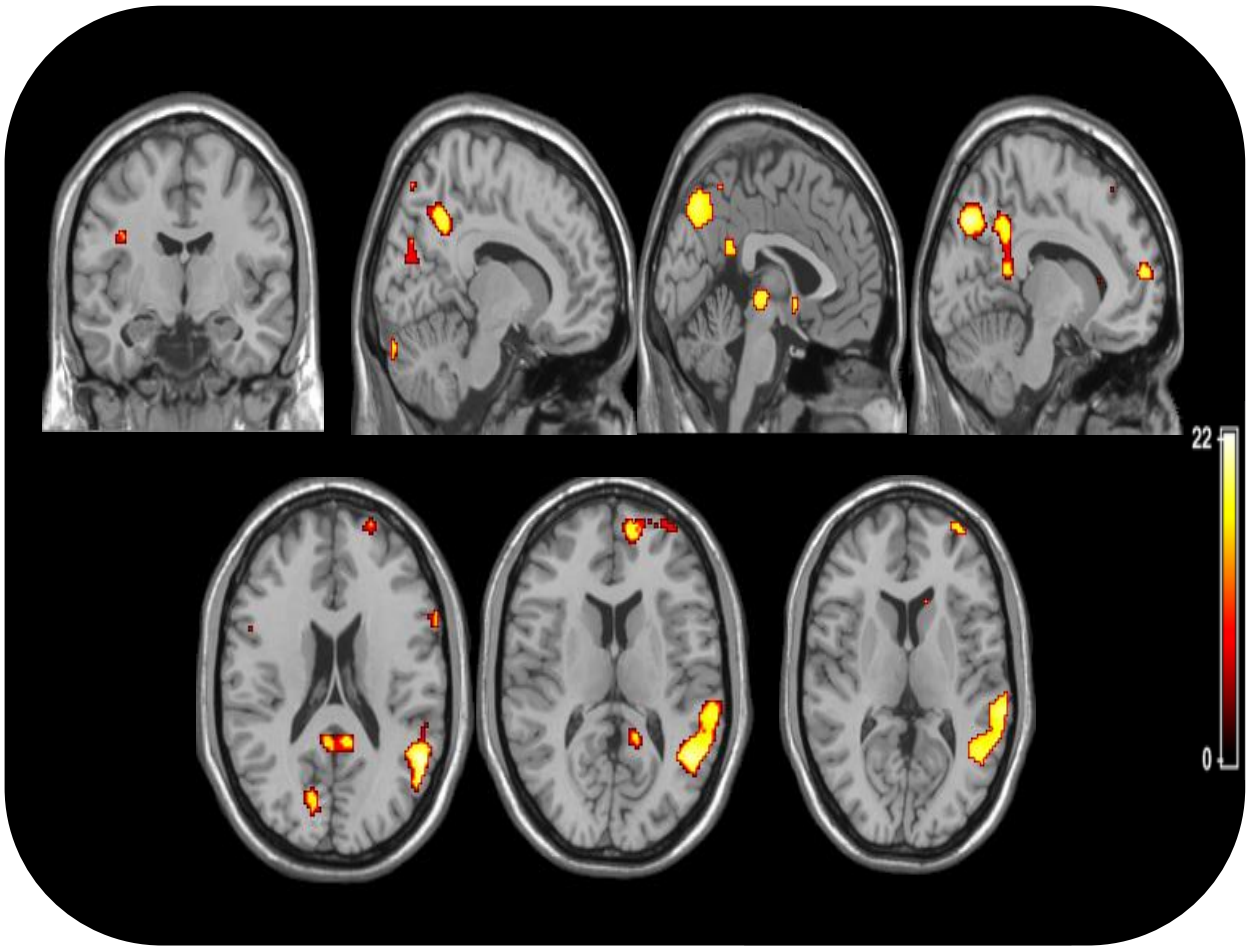

Figure 21: Activation maps in male FEP patients vs male HCs under non-emotional content stimuli. Areas with fMRI response are mainly right precuneus, lelft angular gyrus, inferior and middle temporal lobe and cingulum. (*P*<0.001, uncorrected *k*= 62).

C. Female FEP compared with male FEP patients.

We observed an effect relative to emotional content stimuli between female FEP patients, showed enhanced brain activity compared to male patients in right frontal inferior orbital and orbitofrontal cortex. (*P*<0.001 uncorrected) in Figure 23 and Table 32.

Table 32:Areas of activation in different sex-by-patient's interaction with emotional words.

Females_FEP_emo_vs_males_FEP_emo_group P<0.001 uncorrection			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
5.25	[-22 36 4]	Frontal_inf_Orb_L	Bro_47
5.04	[20 44 -4]	Orbitofrontal_cortex	Bro_11

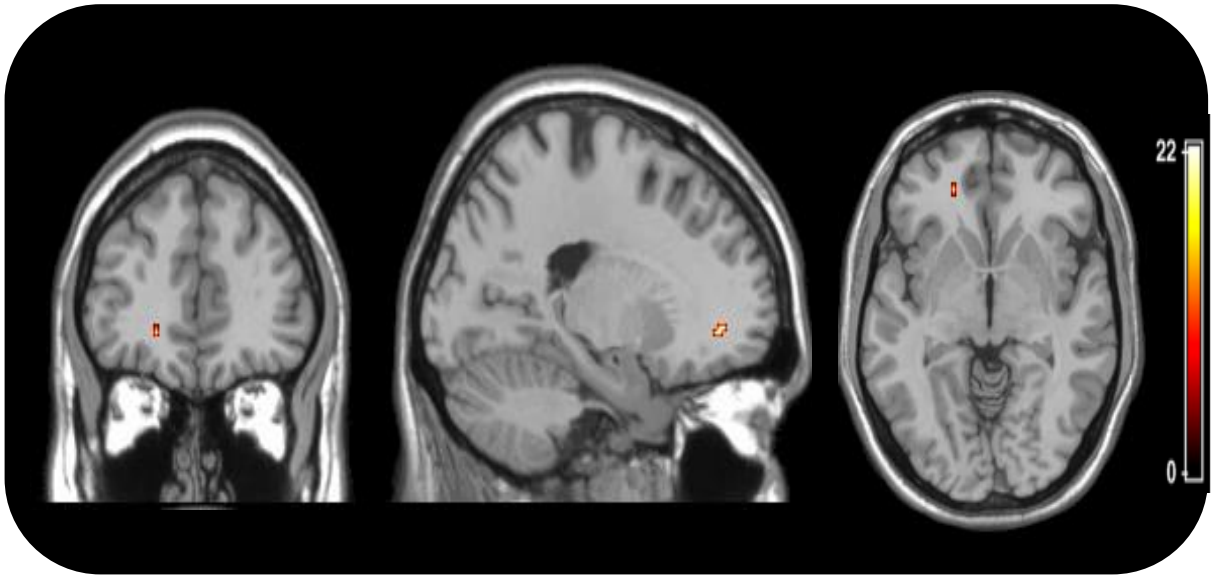

Figure 22:Activation maps in female FEP patients comparing male patietns under emotional content stimuli. (*P*<0.001, uncorrected *k*= 83).

D. Male FEP compared with female FEP patients.

We observed a significant increased activation in FEP Male patients across the left hippocampus and the left superior temporal lobe compared to female patients during emotional content stimuli (Figure 24 andTable 33).

Table 33:Areas of activation in different sex-by-patient's interaction with emotional words.

Males_FEP_emo_vs_females_FEP_emo_group FWE P<0.05 correction			
T_Student	**MNI coordinates**	**Location of avtivation cluster**	**Brodmann´s area**
5.51	[54 -6 -10]	Temporal_Sup_R	Bro_22
4.93	[32 -12 -14]	Hippocampus_R	Bro_20

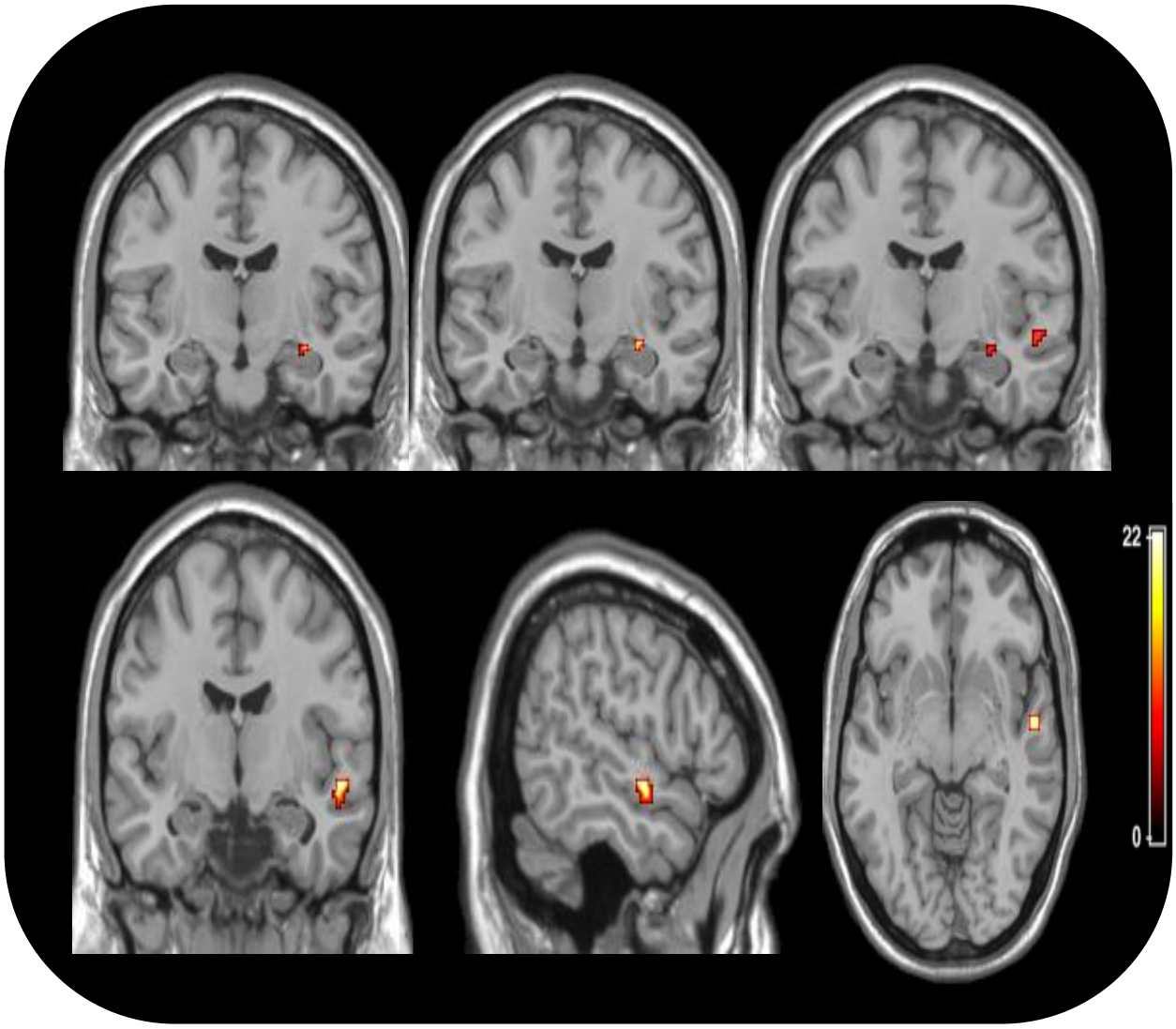

Figure 23: Activation maps in male FEP patients comparing female patietns under emotional content stimuli. (P<0.05 FWE corrected k=24).

CHAPTER IV: DISCUSSION

5. DISCUSSION

5.1 Effects of the auditory paradigm in FEP patients and HCs.

The main result of our study is the enhanced activity of the bilateral amygdala and bilateral hippocampus in FEP patients during the emotional words, in comparison with HCs. In alignment with our hypothesis, we observed that patients compared to HCs had a surge of brain activaty in the limbic system. The areas in which we detected altered activation are consistent also with the hypothesis of processing emotional stimuli through the salience network (Kapur, 2003) and the corticolimbic system which includes the prefrontal cortex, amygdala, hippocampus and striatum (Kober *et al.*, 2008; Bergé *et al.*, 2014; Modinos *et al.*, 2015).

Heightened levels of abnormal activation of the hippocampal regions and amygdala are widely reported in established schizophrenia, in particular in patients presenting with positive psychotic symptoms such as auditory hallucinations (Woodruff, 2004a; González *et al.*, 2006; Sanjuan *et al.*, 2007; Escartí *et al.*, 2010; Liu *et al.*, 2019). The aberrant activation of the hippocampus during processing of emotional and non-emotional words is accordant with a recent systematic review in neuroimaging studies which indicated that functional and neurochemical changes in the frontostriatal circuit and limbic system (amygdala and hipocamppus) play a crucial role in the FEP pathophysiology (Chen *et al.*, 2019).

It is apparent early in the course of psychosis, and evolution of structural abnormalities are detected as the illness evolves (Steen *et al.*, 2006). Recently, Baglivo et al (Baglivo *et al.*, 2018) reported that abnormally low volumes of hippocampal subfield in FEP patients compared to healhy controls are potential neural markers for psychosis onset.

Reduction in the hippocampal volume has been associated with several aspects of the pathophysiology of psychosis, including symptom severity (Watson *et al.*, 2012), cognitive dysfunction (Harrison, 2004) and the lack of insight (Buchy *et al.*, 2010).

Regarding the bilateral increased activity of the amygdala during the emotional paradigm, it is in line with a previous meta-analysis of neuroimages studies which found that amygdala plays a key role in the emotion generation, and is particularly involved in the indentification of emotions (Kober *et al.*, 2008). Also, functional neuroimaging showed that alterations of several forms of salience processing in patients with psychosis in the midbrain substantia nigra/ventral tegmental area, with additional subcortical and cortical regions also showing alterations in salience signalling in psychosis onset (Knolle *et al.*, 2018).

The focus of the amygdala we found to be dysfunctional in FEP patients fairly contains the parahippocampal gyrus, which has been involved in emotional dysfunction in naïve FEP (Knolle *et al.*, 2018).

These fingings are consistent with our hypothesis and align well with prior literature that has consistently reported a prominent role of the aberrant assignment of salience to external objects or internal representations in chronic patietns (Martí-Bonmatí *et al.*, 2007; Sanjuan *et al.*, 2007; Aguilar *et al.*, 2018).

Our results can be considered in light of impaired processing of emotional salience (Kapur, 2003) and with corticolimbic hyperactivation (Hall *et al.*, 2008). In this sense, our data is of interest in light of Kapur´s proposal on the possible mechanism of action of antipsychotics. Kapur postulated that in psychosis a dysregulated dopamine transmission leads to an aberrant assignment of salience to external objects (i.e dysfunctional emotional response to non-emotional stimuli) or internal representation. Subsequent studies have developed this understanding, and it has led to the hypothesis that the dopamine system is altered in psychosis, leading to a dysregulated firing of dopamine neurons and heightened levels of dopamine release (Winton-Brown *et al.*, 2014).

Antipsychotics are efficacious in psychosis because they “dampen salience” of the subjective experience of delusion and hallucinations (Kapur, 2003). In our sample it is noticeable that all the FEP patients have been treated with antipsychotics for a short period. However, our findings are consistent with previous studies showing greater novelty-related fMRI activation in the hippocampus of medicated patients compared with unmedicated patients and healty controls (Tamminga *et al.*, 2012; Ragland *et al.*, 2017).

Even though, studies within ultra-high risk subjects in fMRI showed increased activity in the hippocampus region while performing an emotion judgment task (Seiferth *et al.*, 2008).

There are also similar features for other highly salient stimuli in patients with chronic schizophrenia with persistent hallucinations despite long treatment exposure, showed a clear enhance activity of the frontal lobe, temporal cortex, insula, cingulate, and amygdala was found in comparison with controls (Sanjuan *et al.*, 2007).

Studies indicated that the “salience network” comprises mainly the right anterior insula and dorsal anterior cingulate cortex (Seeley *et al.*, 2007). Furthermore, Modinos et al., (Modinos *et al.*, 2015) found neural correlates of emotional salience elicited activation in different regions of the corticolimbic circuit (prefrontal cortex, inferior frontal gyrus, hypocamppus, amygdala). Recently, Winto-Brown et al., (Winton-Brown *et al.*, 2017) reported that, compared to healty controls, subjects with ultra-high risk for psychosis showed greater activation in the hippocampus contributing to aberrant salience processing and psychotic symptoms. In this line, we speculate a multi-faceted salience network in which different corticolimbic regions can be affected according to their illness stage.

Such experiences to facilitate the description of the multi-faceted salience network, (see Illustration 1) where actual salience refers to a temporary condition of neural activity within the inner the salience network (insula and dorsal anterior cingulate) then generated by the evaluation of external or internal stimuli.

The salience network interacts with the interoceptive pathway (emotional evaluation) by limbic system and frontal and prefrontal executive system to generate the actual salience that prepares one for appropriate behavioural response.

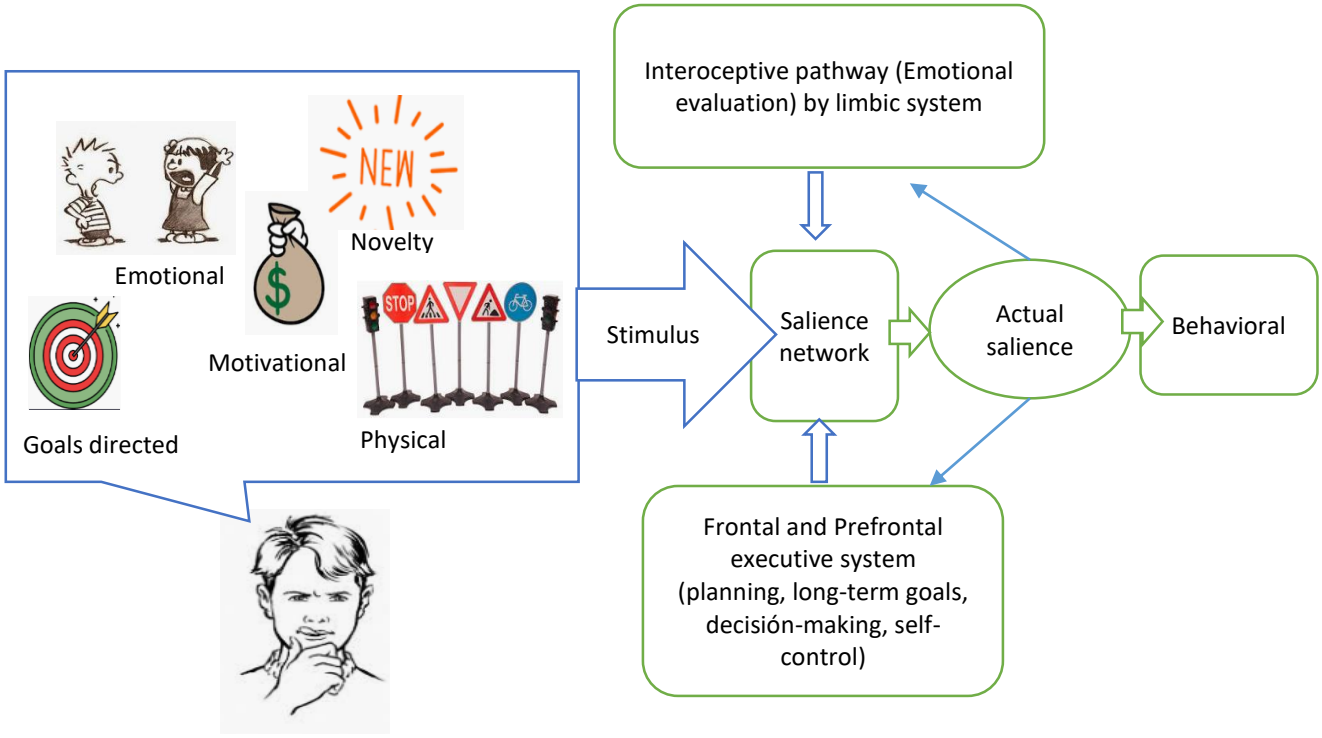

Illustration 1: Adaptated from Palaniyappan et al., 2012 multifaceted salience network and corticolimbic regions during the processing of salience stimulus.

In reference to non-emotionall stimulus in FEP patients an activation of hippocampal areas, meanly left parahippocampus was observed. This finding is in alignment with the aberrant salience hypothesis of psychosis, which is mentioned above, and therefore proposes the following: If dopamine release is dysregulated and coincides with the processing of stimuli that would normally be irrelevant, these may become inappropriately salient (Heinz *et al.*, 2010; Winton-Brown *et al.*, 2017).

Some other brain areas within FEP group were activated whrn listening to emotional words. It shows increased activation in right middle temporal gyrus was reported in FEP patients for emotional words compared to non-emotional words. Furthermore, PANSS negative symptoms factor score reported positive association with right middle temporal gyrus.This data is concordant with the existence evidence of middle temporal gyrus grey matter volume reduction in FEP (Zhang *et al.*, 2018). Also, alteration of the middle temporal gryus have been involved of the network homogeneity of the default mode network (DMN) in schizophrenia onset (Guo *et al.*, 2018) and also has been associated with hallucinations proneness (Hawco *et al.*, 2015). In this sense, our data confirm that middle superior temporal functional alterations in FEP patients represent one key neural factor in the pathophysiology of psychosis. Considering that when HCs enhanced brain activity is involved, it is then the pre-domintantly middle temporal cortex in both conditions, which in healthy subjects, passive listening to speech in respect of prosody caused activation rely on the right temporal cortex (Woodruff, 2004b).

Even though, neuroimaging studies have revealed alterations in emotional processing (Green *et al.*, 2012) and social functioning (Valmaggia *et al.*, 2013) have been documented in FEP patients, as well as, enhanced brain activity in chronic schizophrenia (Sanjuan *et al.*, 2007) , our results provide first evidence that aberrant emotional salience network with limbic regions such as amygdala and mainly right hippocampus compared to HCs may be a key neurobiological mechanism associated with clinical manifestations in the early states of psychosis. Establishing a link

between enhaced activity in emotional processing regions (Modinos *et al.*, 2015) and psychotic symptoms levels may have significant clinical effects.

5.2 Differences in brain activation respect to the meta-analysis.

5.2.1 Insula

Contrary to the results of the meta-analysis in FEP patients described above, we did not find elicited activation in the insula under the auditory emotional paradigm. This result was not a surprise because the insula has been repeatedly shown as an altered cortical region involved in auditory verbal hallucinations (Mallikarjun *et al.*, 2018), prediction error coding (Palaniyappan *et al.*, 2011, 2012; Schmidt *et al.*, 2016) and cognitive tasks which reported increased activation in the insula (Boksman *et al.*, 2005; Benetti *et al.*, 2009; Lencer *et al.*, 2011; Guerrero-Pedraza *et al.*, 2012; Del Casale *et al.*, 2016; Chatterjee *et al.*, 2019; Fan *et al.*, 2019; Park *et al.*, 2019). However, most studies have reported reduced functional activity of the insula in FEP patients relative to healthy controls using different cognitive tasks (Keedy *et al.*, 2015; Schmidt *et al.*, 2016; Dong, Wang, Jia, *et al.*, 2018).

Although there is not a clear explanation for these inconsistent results, we can speculate different reasons for the non-activation, increased and decreased activation in the insula in FEP patients. The primary reason is the influence of the specific paradigm of each study, in the meta-analysis the vast majority of the studies have used cognitive modalities which are more likely to be influenced by attention bias.

Second, the results may depend on the clinical state of the patients at the time of the fMRI, such as their emotional state, positive symptoms and the duration of the illness. The possible effect of antipsychotic medication is also unclear (Fusar-Poli *et al.*, 2013). The third reason to explain this disparity is the heterogeneity in the sample and methodology, particularly in the use of different tasks.

Taken together these findings, indicate that the insula is affected in psychosis, regardless of whether the patients are first-episode or chronic patients. Even if it uses either cognitive or emotional tasks. Particulary, the best explanation for all the data is the model mentioned before which suggest that the key issue in psychosis is related with abnormal “salience” between the emotional and perceptual networks (Kapur, 2003; Modinos *et al.*, 2015; Dong, Wang, Chang, *et al.*, 2018).

5.2.2 Precuneus and cingulate

The results of this study, contradictory to our meta-analysis results we showed an increased activation in male FEP patients compared to male HCs in the precuneus and cingulate under the auditory emotional paradigm.

The precuneus is part of the parietal lobe; the volume of the precuneus has been shown to be decreased in schizophrenia (Bellani *et al.*, 2010). The precuneus has not been one of the primary regions studied by psychosis researchers, who have historically been more interested in frontal and temporal structures. However, a meta-analysis on high risk psychosis revealed the left precuneus to be one of the structures with reduced grey matter volume comparing healthy controls versus high risk patients and high risk patients versus schizophrenia patients (Fusar-Poli *et al.*, 2011).

Functional experiments have shown the precuneus to be part of the default mode network (DMN) (Cavanna *et al.*, 2006).

The precuneus is an association area with wide-spread extra parietal connections, and there is evidence that the fronto-parietal control network is disrupted in psychosis (Baker *et al.*, 2014).

In other words, the precuneus has been recently shown to alter the DMN in the first episode of psychosis (Rikandi *et al.*, 2018) and in FEP during auditory verbal hallucinations (Mallikarjun *et al.*, 2018). This alteration in DMN intrinsic activity is associated with poor cognitive function in deficit schizophrenia (Zhou *et al.*, 2019). In addition, in un-medicated patients, a decrease in functional connectivity between the hippocampus and precuneus has been demonstrated (Kraguljac *et al.*, 2014).

This structure has an important role in memory retrieval and self-related visuospatial imagery (Cavanna *et al.*, 2006), both of which have been shown to be altered in psychosis.

Regarding the cingulate, bain activation under emotional auditory content was observed with opposite direction of the results of the meta-analysis. There may be serveral explanations for these contradictory findings. First, differences in the stimuli due to the vast majority of the studies analyzed in the meta-analysis have used different cognitive tasks. Second, the sample size may have played an important role. The patient sample used in this study was larger than those used in the studies.

Third, differences in the methodology may explain the differences in the cingulate activation since many of the meta-analysis´ studies used mainly visual tasks in every form of paradigm.

In spite of that, our finding show that cingulate was an area involved when male FEP patients were presented high emotional content stimuli is concordant with a recent study where the cingulate displayed a significant increased activation following the treatment (Blessing *et al.*, 2019).

Therefore, it is possible that these areas represent mal-functioning cortical regions which are more active in FEP patients under the auditory emotional paradigm. This hyper-activation within these areas in addition to salience network may play an important role in reduce the threshold of significance. However, little is known about sex differences in FEP patients, therefore, given these resutls entirely in the male sample this findings will require more systematic testing for confirmation.

5.3 Differences in brain activation between FEP and chronic patients during fMRI tasks.

The results of this study were partly in accordance with the study of our group in patients with schizophrenia patients (Sanjuan *et al.*, 2007; Escartí *et al.*, 2010). They found a clear enhanced activity of the frontal lobe, temporal cortex, insula, cingulate and amygdala (mainly right side) with emotional auditory paradigm. In this study we found enchanced activity in all these areas under the emotional words except the insula.

Moreover, we found in FEP patients a significant enhanced bilateral activity in the hipocamppus and amygadala between emotional vs non-emotional words. Notably, Talati et al (Talati *et al.*, 2015), found the hippocampal excitation-inhibition imbalances in early stage of psychosis might lead to a greater hippocampal metabolic demand in the chronic stage (Zhao *et al.*, 2018).

Our results indicate a different pattern of brain activation in FEP patients compared with chronic patients with hallucinations, suggesting that the onset of illness is signigicantly associated with lymbic hyperactivity. Therefore, functional alterations may be more marked in specific stages of the disorder or are diverse in specific subgroups (e.g. patients with good vs poor insight).

However, our results based on an auditory emotional paradigm showed the opposit that other studies using cognitive and emotional paradigms in FEP patients (Mwansisya *et al.*, 2017). Our group also found important differences in activation in a systematic review of longitudinal FEP samples. The study showed a pattern of predominantly hypoactivation in several brain areas at baseline that may normalize to a certain extent after treatment. However, The results should be interpreted with caution given the small number of studies and their methodological and clinical heterogeneity (González-Vivas *et al.*, 2019)-

Taken toghter, there could be two main reasons for these differences. The first one is the heterogeneity in methodology, the type of paradigm selected is a key to understanding fMRI results (Cao *et al.*, 2018). Different paradigms have been

reported different brain regions (Zhou *et al.*, 2014). In general, visual and cognitive tasks reported reduce activation because of are more likely to be influenced by attention bias and auditory and emotional tasks increased activation because of the symptom profile. The second reason to consider is the adversity of determining the time interval between symptom onset and the first clinical assessment and treatment. Psychotic episodes sometimes start with negative symptoms, which are often hard to place along a timeline.

5.4 Sex differences observed in the fMRI activation

As a result of the observe differences in sex we decided to use this variable as covariate to explore effects with auditory emotional paradigm in the fMRI vowel-wise analyses.

We did not observe any great differences between FEP patients and HCs group under the emotional content stimuli. However, we found fairly significant enhanced activation in the hippocampus in male patients as compared to female FEP patients in the emotional content stimuli. Similar results have been demonstrated in FEP patients that indicate in males at FEP have a greater risk of conversation to psychosis than females (Pruessner *et al.*, 2015).

A recent study revealed smaller hippocampal volume in male compared with female in ultra-high risk subjects (Guma *et al.*, 2017; Pruessner *et al.*, 2017) demonstrating sex specific alteration in hippocampal volume that are closely related to psychotic symptoms.

In addition, females at FEP showed increased activation during emotional and non-emotional stimuli. Specifically, we found that female patients show increased activity in right frontal inferior orbital and orbitofrontal cortex whereas males at FEP did not show activation in these regions. These results can be interpreted in the context of a neurobiological defect within the corticolimbic brain regions involving the hippocampus and the prefrontal cortex. In turn, prefrontal control may be essential in modulating the deliberative responses driven by limbic interactions (Likhtik *et al.*, 2005; Phelps *et al.*, 2005; Wojtalik *et al.*, 2017; Wang *et al.*, 2018; Widmayer *et al.*, 2018).

Taken together, sex differences in brain activity suggests more alteration or diffuse dysfunction in fronto-limbic regions among men. The validity of these effects of sex on FEP patients may have important consequences for understanding the nature of the illness. That is, if there are significant differences in the functional brain activity, neuroanatomy (Guma *et al.*, 2017), and course of illness (Jongsma *et al.*, 2018), maybe men and women are at different risks for expressing different subtypes of psychosis.

5.5 Limitations and strengths.

It has to be noted that this study is subject to some limitations. First and foremost, the cross-sectional nature of our study prevents conclusions that might otherwise be observed through a longitudinal study.

Second, the marked difference across age and sample size of male in the healthy control group and the smaller number of females at FEP compromised the statistical power to detect significant associations in these subgroups. Third, the sample was heterogeneous in terms of socio-demographical data but the sample was homogeneous in terms of the category of psychotic disorder.

Fourth, all FEP patients were on medication mostly with second generation antipsychotics at the time of the respective study, and there was no standardization of medications or doses, which could clearly affect the results. Thus, it cannot be omitted that medication dose had an impact on brain activity, however dysfunctions in emotional processing can be unaffected by antipsychotics in FEP patietns (Schneider *et al.*, 2007; Modinos *et al.*, 2015) and antipsychotic effects have been reported on fMRI activation referred to executive and memory function (Fusar-Poli *et al.*, 2007). Moreover, dysfunction in limbic regions involving emotional processing have been obtained previously in FEP antipsychotic-naïve patients (Bergé *et al.*, 2014).

Fifth, by correcting for false positive (*P*<.05 FWE vowel-level correction or *P*<.001 uncorrected) we achieved no grand results in some fMRI analysis. Sixth, the results are only generalizable to individuals who had been diagnosed with a psychotic disorder for the first time and not to all patients diagnosed with chronic psychosis. The clinical heterogeneity of psychosis is beyond the scope of this study.

Lastly, we report statistically significant results from sex difference testing the impact of neural activity under emotional and non-emotional content stimuli, even though caution is necessary in interpreting these findings due to the small female sample size in FEP patients. However, the results of the present study, following the project that started in 2005 indicate new evidence of limbic alterations that extend finding with previous imaging studies in chronic schizophrenia with the same auditory emotional paradigm (González *et al.*, 2006; Martí-Bonmatí *et al.*, 2007; Sanjuan *et al.*, 2007; Escartí *et al.*, 2010; Aguilar *et al.*, 2018; Escarti *et al.*, 2019).

In spite of the above limitations, this study provides relevant information to understand the dysfuntion of the emotional response in FEP patients. The study uses a rigorous approach to analyse the brain activity during emotional fMRI auditory paradigm. We found confirmatory evidence of enhanced limbic activity in FEP patients under emotional and non-emotional words. Later then added to this core by finding and indicating that this alteration is consistent with other studies suggesting a relevant role for emotional response in the pathogenesis and treatment of psychosis.

6. CONCLUSION.

1. Concretely, these findings suggest that limbic system impairment (mainly hippocampus and amygdala) in FEP patients are a core alteration that are present early in the disorder. It may firmly serve as a biological imaging marker for emergence of the emotional response in FEP patients.

2. FEP patients and HCs activated different brain areas during emotional auditory paradigm. FEP patients, mostly activated under emotional content stimuli superior temporal gyrus, right middle temporal gyrus, bilateral amygdala and bilateral hippocampus, whereas during non-emotional stimuli left middle temporal gyrus and left parahippocampal area were activated in FEP patients. This corticolimbic changes in fMRI activity during emotional processing are concordant with the previous finding, and may be associated with the emotional disorder and cognitive alterations in FEP patients.

3. Alteration in emotional fMRI auditory paradigm between FEP and chronic patients are different in specific stages of the disorder and might be more noticeable during certain stages.

4. Increased activation during emotional task may suggest a hemodynamic dysfunctions associated with different functional changes in limbic regions (hippocampus and amygdala), while considering psychosis as a continuum of changes starting from mild emotional and cognitive impairments to serious psychotic symptoms.

5. We suggest that abnormal salience activation may involve diferently corticolimbic areas depending on illness stage during emotional auditory paradigm.

6. Emotional dysfunction in the hippocampal areas (mainly right side) are perturbed from the earliest expression of the disorder in FEP patients.

7. The pattern of brain activity in FEP patients appears to be dependent of sex or functional alterations on appearance of psychotic symptoms.

8. A better understanding of brain activity in sex differences may help in developing new biomarkers that are not currently related to neuropsychiatric illness and FEP population. This area of research needs more investigation, to comprehend why males and females who are in the same diagnosis may carry a different disease.

9. Going further, longitudinal studies are needed in larger samples and simple and more replicable paradigms. Consequently, it is needed to shed more light on the potential of emotion processing deficits as trait biomarkers of vulnerability to point at new directions for early interventions.

CHAPTER V: REFERENCES AND ANNEX

7. REFERENCES

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8. ANNEXES

ANNEX I: Data collection booklet at First-Episode Psychosis Unit of the Hospital Universitarí Clínic of Valencia.

First-Episode Psychosis Unit of the Hospital Universitario Clínico of Valencia.

CUADERNO DE RECOGIDA DE DATOS INICIAL

Paciente:
NHC:
SIP:

Fecha evaluación:

INFORMACIÓNSOBRE INCLUSIÓN EN EL PROGRAMA

Yo Don/doña_____ con DNI_____ he sido informado de la inclusión en el Programa de Primeros Episodios Psicóticos (Hospital Clínico Universitario de Valencia). Este programa es un programa específico para atender a pacientes con un primer episodio psicótico durante los primeros años de la enfermedad en el denominado periodo crítico, en el que se le atenderá durante el periodo necesario para realizar un abordaje integral de los síntomas que presenta (con una duración máxima de 3 años).

Nombre y firma del paciente o responsable legal:

En Valencia, a _____de_____ del 20__

IDENTIFICACIÓN PACIENTE

1. **Paciente** _____
2. **SIP**
3. **Fecha de nacimiento:** ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋
4. **Edad:** ☐☐ años
5. **Sexo:** 1. Mujer
   2. Varón
6. **Fecha de inclusión:** ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋
7. **Teléfono** _____ _____

HISTORIA CLÍNICA

1. DERIVACIÓN

☐ 1. Hospital Clínico SALA

☐ 2. Hospital Clínico urgencias

☐ 3. CSM FOIOS

☐ 4. CSM MALVARROSA

☐ 5. UHD

☐ 6. INTERCONSULTA

☐ 7. PRIMARIA

☐ 8. OTROS_____

2. DATOS SOCIODEMOGRAFICOS

Etnia:

☐ 0. Caucásica

☐ 1. Gitana

☐ 2. Magrebí

☐ 3. Subsahariana

☐ 4. Asiática

☐ 5. Caribeña

☐ 6. Hispana

☐ 7. Otras

☐ 99.Desconocido

Estado Civil:

1. Soltero/a

2. Casado-a

3. Divorciado-a / separado-a

4. Viudo-a

5. Convivencia > 6 meses

HISTORIA CLÍNICA

Nivel Educativo (Estudios Universitarios):

1. Analfabetismo
2. Estudios primarios/EGB
3. ESO/FP1 (hasta 16 años)
4. Bachillerato/FP2/BUP/COU (hasta 18 años)
5. Estudios universitarios
6. Desconocido

Situación Laboral:

1. Activo
2. Paro con subsidio
3. Paro sin subsidio
4. Invalidez
5. Estudiante
6. Jubilado

Convivencia:

1. Solo
2. Familia origen
3. Familia propia
4. Descendientes
5. Institución
6. Sin domicilio
7. Otros (especificar): _____

HISTORIA CLÍNICA

3. HABITOS TÓXICOS

Tabaco: 1. Sí 2. No
Edad de inicio

Alcohol: 1. Sí 2. No

Edad de inicio
*Especificar*_____
_____

Cannabis:1. Sí 2. No Especificar unidades/día: ☐☐
Edad de inicio

Otros:

1. Cocaina
2. Alucinógenos
3. MDMA (Extasis)
5. Anfetaminas
6. Ketamina
7. Heroína
8. Otros

Edad inicio

4. ANTECEDENTES FAMILIARES

¿Tiene el paciente antecedentes psiquiátricos en familiares de primer grado?

0. No valorable
1. Posible
2. Seguro

DIAGNOSTICO

¿Tiene el paciente antecedentes psicosis en familiares de primer grado?

0. No valorable
1. Posible
2. Seguro

5. PATOLOGÍA PSIQUIÁTRICA (en la inclusión del programa)

4.
- ☐ F20 Esquizofrenia
- ☐ F22 Trastornos de ideas delirantes persistentes
- ☐ F23 Trastornos psicóticos agudos y transitorios
- ☐ F24 Trastornos de ideas delirantes inducidas
- ☐ F25 Trastornos esquizofrénicos
- ☐ F28 Trastornos Otros trastornos psicóticos no orgánicos
- ☐ F29 Psicosis no orgánica sin especificación
- ☐ F30 Episodio maníaco
- ☐ F31 Trastorno bipolar

6. FACTORES DE RIESGO

- Urbanicidad

☐ 1. si

☐ 2. no

-Inmigración

☐ 1. si

☐ 2. no

-Trauma (en otro, añadir cual)

0. No valorable
1. Posible
2. Seguro

HISTORIA CLÍNICA

7. DIAGNOSTICO

Fecha de Inicio de Síntomas:

☐ 1. No valorable

☐ 2. Fecha ___/___/___

Fecha de Primer Diagnóstico/tratamiento:

☐ 1. No valorable

☐ 2. Fecha ___/___/__

TRATAMIENTO (si previo o en la inclusión):

- **ANTIPSICÓTICOS (nombre/dosis):**

0. No tratamiento
1. Típicos _____
2. Atípicos _____

_ NOMBRE TRATAMIENTO:

1. Amisulpride
2. Aripiprazol
3. Clorpromacina
4. Clotiapina
5. Clozapina
6. Fluefenazina
7. Flupentixol
8. Haloperidol
9. Levomepromazina
10. Loxapina
11. Olanzapina
12. Perfenazina

- ☐ 16. Quetiapina
- ☐ 17. Risperidona
- ☐ 18. Sulpirida
- ☐ 19. Tiaprida
- ☐ 20. Tioproperazina
- ☐ 21. Tioridazina
- ☐ 22. Trifluoperazina
- ☐ 23. Ziprasidona
- ☐ 24. Zuclopentixol

– **ANTICOLINÉRGICOS :**

- ☐ 1. SÍ _____
- ☐ 2. No

– **BENZODIAZEPINAS :**

- ☐ 1. SÍ _____
- ☐ 2. No

– **ANTIDEPRESIVOS :**

1. SÍ _____
2. No

– **EUTIMIZANTES :**

- ☐ 1. SÍ _____
- ☐ 2. No

TRATAMIENTO MÉDICO (SÓLO SI HA INTERFERIDO EN EL EPISODIO)

MOTIVO_____

INICIO_____

CESE _____

8. TENTATIVAS DE SUICIDIO

¿Ha realizado el paciente alguna tentativa de suicidio?

1. NO
2. SÍ → Nº Tentativas: _____

9. ENFERMEDADES MÉDICAS ASOCIADAS

1. No presenta
2. Respiratorias
3. Infecciosas
4. Digestivas
5. Inmunológicas
6. Hematológicas-oncológicas
7. Neurológicas
8. Endocrino-metabólicas
9. Cardiovasculares
10. Otras: _____

IMPRESIÓN CLÍNICA GLOBAL DE SEVERIDAD (CGI-SI)

Según su experiencia clínica en este paciente, con referencia a su grupo de población, ¿qué grado de enfermedad presenta el paciente en este momento?

1. Normal, sin enfermedad
2. Enfermedad mínima
3. Levemente enfermo
4. Moderadamente enfermo
5. Notablemente enfermo
6. Gravemente enfermo
7. Extremadamente enfermo

ESCALA DE EVALUACIÓN GLOBAL DEL FUNCIONAMIENTO (GAF)

Hay que considerar la actividad psicológica, social y laboral a lo largo de un hipotético continuum de salud-enfermedad. No hay que incluir alteraciones de la actividad debidas a limitaciones físicas (o ambientales).

100-91	**Actividad satisfactoria en una amplia gama de actividades, nunca parece superado por los problemas de su vida, es valorado por los demás a causa de sus abundantes cualidades positivas. Sin síntomas.**
90-81	**Síntomas ausentes o mínimos** (p.ej., ligera ansiedad antes de un examen), **buena actividad en todas las áreas, interesado e implicado en una amplia gama de actividades, socialmente eficaz, generalmente satisfecho de su vida, sin más preocupaciones o problemas que los cotidianos** (p ej., una discusión ocasional con miembros de la familia).
80-71	**Si existen síntomas, son transitorios y constituyen reacciones esperables ante agentes estresantes psicosociales** (p.ej., dificultades para concentrarse tras una discusión familiar); **sólo existe una ligera alteración de la actividad social, laboral o escolar** (p.ej., descenso temporal del rendimiento escolar).
70-61	**Algunos síntomas leves** (p.ej., humor depresivo e insomnio ligero), **o alguna dificultad en la actividad social, laboral o escolar** (p.ej., hacer novillos ocasionalmente o robar algo en casa), **pero en general funciona bastante bien, tiene algunas reacciones interpersonales significativas.**
60-51	**Síntomas moderados** (p.ej., afecto aplanado y lenguaje circunstancial, crisis de angustia ocasionales) **o dificultades moderadas en la actividad social, laboral o escolar** (p.ej., pocos amigos, conflictos con compañeros de trabajo o de escuela).
50-41	**Síntomas graves** (p.ej., ideación suicida, rituales obsesivos graves, robos en tiendas) **o cualquier alteración grave de la actividad social, laboral o escolar** (p.ej., sin amigos, incapaz de mantenerse en un empleo).
40-31	**Una alteración de la verificación de la realidad** (p.ej., el lenguaje es a veces ilógico, oscuro o irrelevante) **o de la comunicación o alteración importante en varias áreas como el trabajo escolar, las relaciones familiares, el juicio, el pensamiento o el estado de ánimo** (p.ej., un hombre depresivo evita a sus amigos, abandona la familia y es incapaz de trabajar; un niño golpea frecuentemente a niños más pequeños, es desafiante en casa y deja de acudir a la escuela).
30-21	**La conducta está considerablemente influida por ideas delirantes o alucinaciones o existe una alteración grave de la comunicación o el juicio** (p.ej., a veces es incoherente, actúa de manera claramente inapropiada, preocupación suicida) **o incapacidad para funcionar en casi todas las áreas** (p.ej., permanece en la cama todo el día; sin trabajo, vivienda o amigos).
20-11	**Algún peligro de causar lesiones a otros o a sí mismo** (p.ej., Intentos de suicidio sin una expectativa manifiesta de muerte; frecuentemente violento; excitación maníaca), **u ocasionalmente deja de mantener la higiene personal mínima** (p.ej., con manchas de excrementos), **o alteración importante de la comunicación** (p.ej., muy incoherente o mudo).
10-1	**Peligro persistente de lesionar gravemente a otros o a sí mismo** (p.ej., violencia recurrente), **o incapacidad persistente para mantener la higiene personal mínima o acto suicida grave con expectativa manifiesta de muerte.**
0	**Información inadecuada.**

PUNTUACIÓN TOTAL: ☐☐☐

PARA LA ESQUIZOFRENIA (PANSS)

1) SUBESCALA POSITIVA:

P1	Delirios	1	2	3	4	5	6	7
P2	Desorganización conceptual	1	2	3	4	5	6	7
P3	Conducta alucinatoria	1	2	3	4	5	6	7
P4	Excitación	1	2	3	4	5	6	7
P5	Grandiosidad	1	2	3	4	5	6	7
P6	Suspicacia / persecución	1	2	3	4	5	6	7
P7	Hostilidad	1	2	3	4	5	6	7

Subtotal:

2) SUBESCALA NEGATIVA:

N1	Afecto embotado	1	2	3	4	5	6	7
N2	Retirada emocional	1	2	3	4	5	6	7
N3	Disminución de la simpatía	1	2	3	4	5	6	7
N4	Retirada social apática/pasiva	1	2	3	4	5	6	7
N5	Dific. para pensar en abstracto	1	2	3	4	5	6	7
N6	Dific. para la conversación fluida	1	2	3	4	5	6	7
N7	Pensamiento estereotipado	1	2	3	4	5	6	7

Subtotal:

3) SUBESCALA PSICOPATOLOGIA GENERAL:

G1	Preocupación somática ……	1	2	3	4	5	6	7
G2	Ansiedad	1	2	3	4	5	6	7
G3	Sentimientos de culpa	1	2	3	4	5	6	7
G4	Tensión	1	2	3	4	5	6	7
G5	Manierismos y actitud postural	1	2	3	4	5	6	7
G6	Depresión	1	2	3	4	5	6	7
G7	Retraso motor ..... ……	1	2	3	4	5	6	7
G8	Falta de cooperación	1	2	3	4	5	6	7
G9	Pensamientos inusuales	1	2	3	4	5	6	7
G10	Desorientación	1	2	3	4	5	6	7
G11	Atención deficiente	1	2	3	4	5	6	7
G12	Falta de juicio y discernimiento	1	2	3	4	5	6	7
G13	Alteración de la voluntad	1	2	3	4	5	6	7
G14	Deficiente control de los impulsos	1	2	3	4	5	6	7
G15	Preocupación ..... ……	1	2	3	4	5	6	7
G16	Evitación social activa	1	2	3	4	5	6	7

Subtotal:

PUNTUACIÓN TOTAL:

ANNEX II: The Medical Ethics Committee

INFORME DEL COMITE ETICO DE INVESTIGACION CLINICA DEL HOSPITAL CLINIC UNIVERSITARI DE VALENCIA

Don Diego V. Cano Blanquer, Secretario del Comité Ético de Investigación del Hospital Clínic Universitari de Valencia

CERTIFICA

Que en este Comité, en su reunión de fecha 27 de febrero de 2018, y según consta en el acta de la misma, se han analizado los aspectos éticos y científicos relacionados al proyecto de investigación que lleva por título:

Resonancia magnética funcional y expresión génica como marcadores predictivos en Primeros Episodios Psicóticos.

Mismo que será llevado a cabo en el Servicio de Psiquiatría y cuyo investigador principal es el Dr. Julio Sanjuan Arias, acordando que reúne las características adecuadas referentes a información a los pacientes y cumplimiento de los criterios éticos para la investigación médica y biomédica establecidos en la ***Declaración de Helsinki*** (Junio 1964, Helsinki, Finlandia) de la Asamblea Médica Mundial, y sus revisiones (Octubre 1975, Tokio, Japón), (Octubre 1983, Ve necia, Italia), (Septiembre 1989, Hong Kong), (Octubre 1996, Somerset West, Sudáfrica), (Octubre 2000, Edimburgo), (Octubre 2008 Seúl, Corea) y (Octubre 2013 Fortaleza, Brasil) y en la ***Declaración Universal sobre el Genoma Humano y los Derechos del Hombre de la UNESCO*** y los acuerdos del ***Protocolo Adicional del Consejo de Europa para la protección de los Derechos del Hombre y de la dignidad del ser humano frente a la aplicaciones de la biología y de la medicina*** (París 12-1-1998, ratificado el 23-7-1999).

Lo que certifico a efectos oportunos de la convocatoria de Ayudas a Proyectos de Investigación en Salud del Instituto de Salud Carlos III 2017.

Valencia, 27 de febrero de 2018.

Fdo. : Don Diego V. Cano Blanquer
Secretario del Comité Ético de Investigación Clínica

GENERALITAT VALENCIANA

DEPARTAMENT CLÍNIC MALVA-ROSA

Hospital Clínic Universitari

JULIO SANJUAN ARIAS
Servicio de Psiquiatría

Valencia, 02 de marzo de 2018

Estimado Dr. Sanjuan ,

El motivo de la presente es informarle que en la pasada reunión del Comité de Ética del Hospital Clínico Universitario de Valencia de fecha 27 de febrero de 2018, ha sido evaluado el proyecto titulado "Resonancia magnética funcional y expresión génica como marcadores predictivos en Primeros Episodios Psicóticos." del cual usted es el investigador principal.

En dicha evaluación, se acordó informar favorablemente.

Así mismo, se le informa que la legislación vigente en investigaciones donde se va a proceder a la toma de muestras de pacientes, es la Ley 14/2007 de 3 de julio, de Investigación Biomédica y estas investigaciones deberán cumplir dicha normativa.

En caso de requerir información adicional, no dude en ponerse en contacto con la secretaría del Comité.

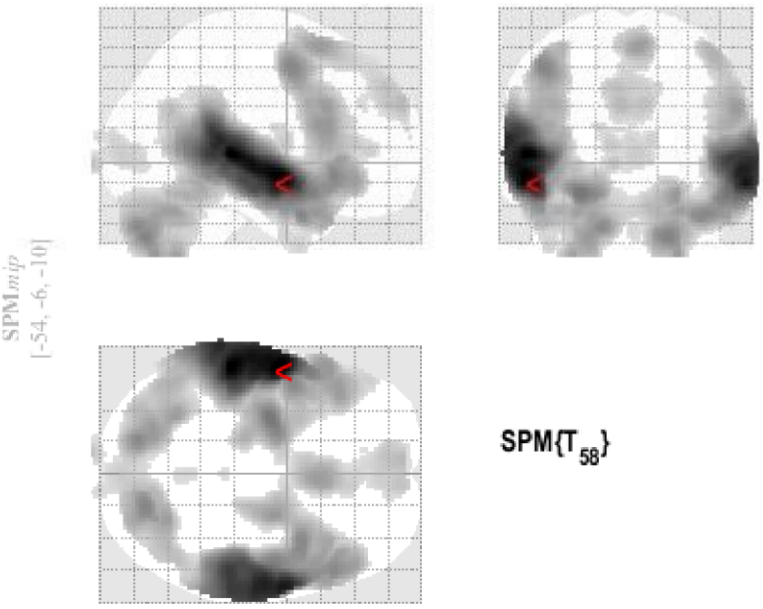
Sin otro particular, reciba un cordial saludo.

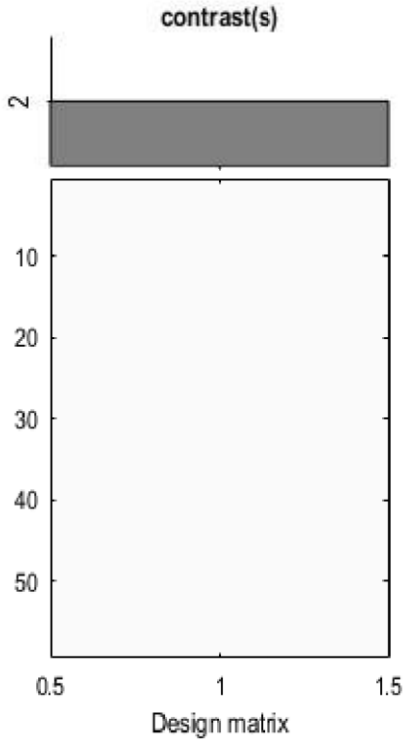
Marina Soro

Dra. Marina Soro Domingo
Presidenta del Comité Ético de Investigación

ANNEX III: Activation maps SPM

FEP_emotional_task_group





SPMresults: .\FEP\EMO

Height threshold T = 4.772919 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}			
0.000	12	0.000	0.000	19911	0.000	0.000	0.000	14.17	Inf	0.000	-54	-6	-10
						0.000	0.000	14.00	Inf	0.000	-56	-30	2
						0.000	0.000	13.22	Inf	0.000	-60	-20	-4
		0.000	0.000	9538	0.000	0.000	0.000	12.96	Inf	0.000	62	-4	-12
						0.000	0.000	12.54	Inf	0.000	60	-14	-6
						0.000	0.000	11.51	Inf	0.000	60	-32	2
		0.000	0.000	2060	0.000	0.000	0.000	7.50	6.25	0.000	4	16	60
						0.000	0.010	6.35	5.51	0.000	-6	60	28
						0.001	0.030	5.99	5.27	0.000	8	60	30
		0.008	0.238	52	0.158	0.001	0.030	6.00	5.27	0.000	-8	-106	-2
		0.002	0.103	116	0.043	0.004	0.101	5.61	4.99	0.000	-10	-4	8
						0.016	0.378	5.15	4.66	0.000	-14	-6	16
		0.000	0.001	507	0.000	0.004	0.101	5.60	4.99	0.000	2	-90	2
						0.028	0.605	4.97	4.51	0.000	12	-104	2
						0.030	0.626	4.95	4.50	0.000	10	-102	14
		0.007	0.238	56	0.144	0.006	0.166	5.45	4.87	0.000	12	-2	10
		0.006	0.226	67	0.113	0.018	0.424	5.11	4.63	0.000	2	-56	-36
		0.027	0.722	10	0.541	0.026	0.591	4.99	4.53	0.000	-44	38	30
		0.031	0.740	7	0.616	0.029	0.605	4.96	4.51	0.000	2	-36	-2
		0.034	0.741	5	0.679	0.035	0.714	4.90	4.46	0.000	-18	-104	12

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.77, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 27.642
Expected number of clusters, <c> = 0.05
FWEp: 4.773, FDRp: 5.960, FWEc: 2, FDRc: 507

Degrees of freedom = [1.0, 58.0]
FWHM = 19.7 18.9 18.6 mm mm mm; 9.9 9.4 9.3 {voxels}
Volume: 1535184 = 191898 voxels = 206.4 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 863.56 voxels)

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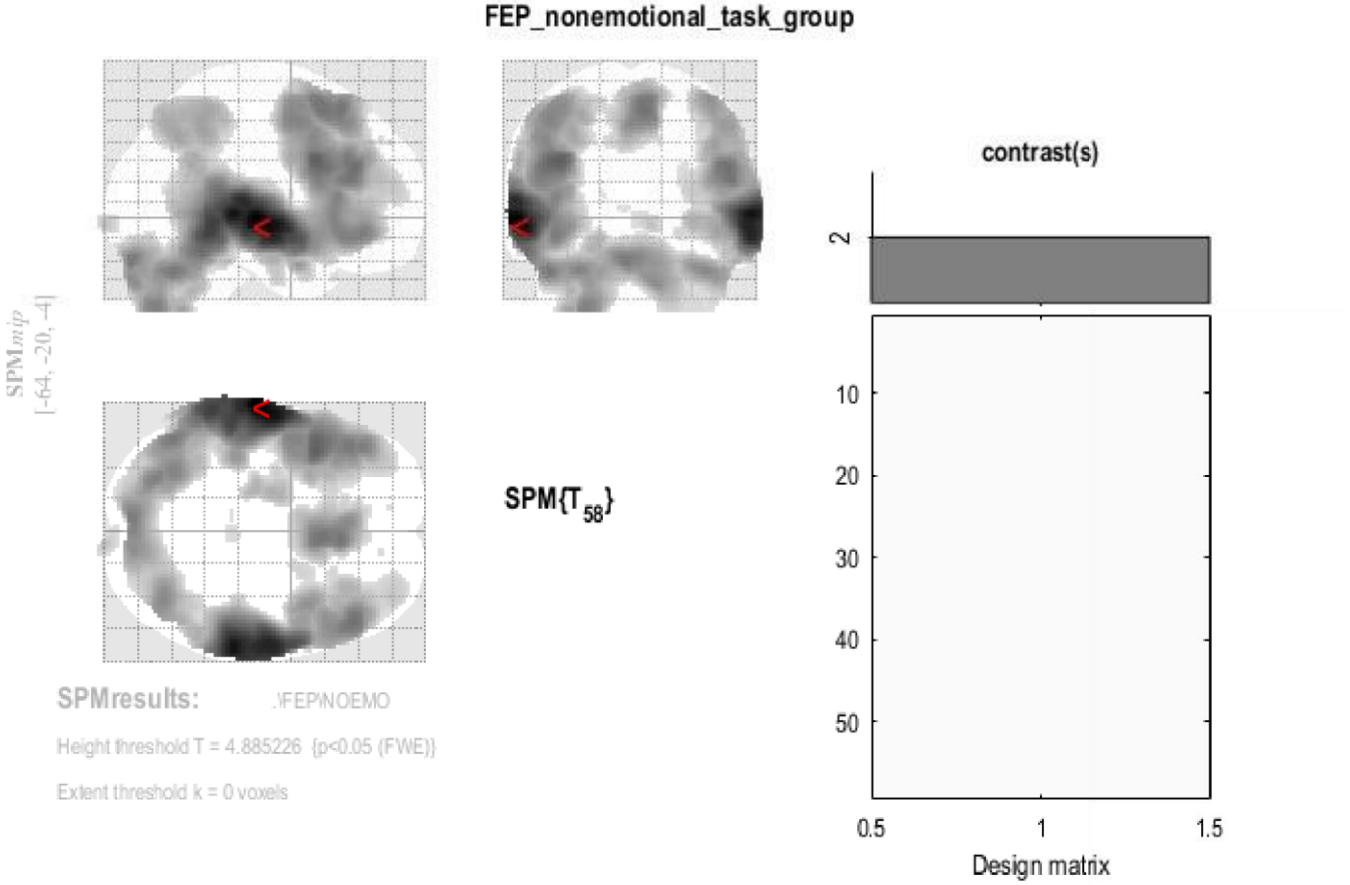


Statistics: ***p-values adjusted for search volume***

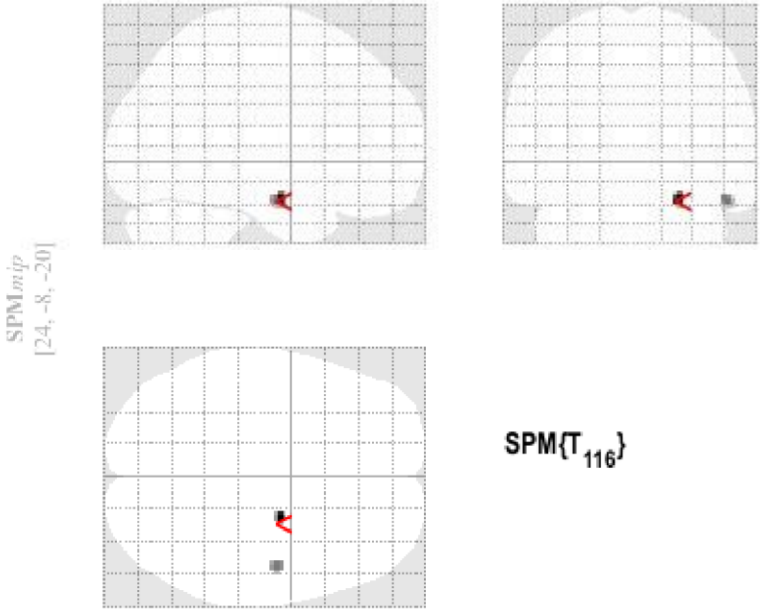
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*T*	($Z_{=}$)	p_{uncorr}			
0.000	10	0.000	0.000	38233	0.000	0.000	0.000	15.60	Inf	0.000	-64	-20	-4
						0.000	0.000	14.35	Inf	0.000	62	-32	0
						0.000	0.000	13.70	Inf	0.000	62	-14	-6
		0.000	0.000	512	0.000	0.000	0.002	6.89	5.87	0.000	52	-40	52
						0.001	0.021	6.16	5.38	0.000	40	-58	50
						0.017	0.370	5.25	4.73	0.000	58	-44	36
		0.003	0.132	68	0.053	0.000	0.011	6.36	5.52	0.000	8	-102	-6
		0.000	0.025	146	0.007	0.001	0.029	6.07	5.32	0.000	38	6	-28
						0.007	0.161	5.52	4.93	0.000	24	4	-24
		0.011	0.442	25	0.221	0.019	0.400	5.21	4.70	0.000	4	-32	-2
		0.035	0.756	3	0.693	0.023	0.475	5.15	4.65	0.000	14	46	40
		0.035	0.756	3	0.693	0.026	0.526	5.11	4.62	0.000	38	20	-34
		0.032	0.756	4	0.641	0.041	0.836	4.95	4.50	0.000	-6	-34	2
		0.038	0.756	2	0.756	0.042	0.839	4.95	4.50	0.000	-10	52	38
		0.038	0.756	2	0.756	0.046	0.922	4.91	4.47	0.000	-16	-2	10

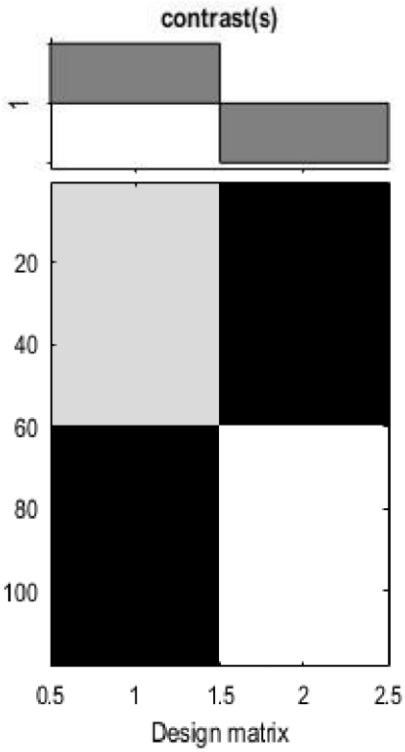
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.89, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 17.911
Expected number of clusters, <c> = 0.05
FWEp: 4.885, FDRp: 5.998, FWEc: 2, FDRc: 146

Degrees of freedom = [1.0, 58.0]
FWHM = 17.6 16.7 16.3 mm mm mm; 8.8 8.3 8.2 {voxels}
Volume: 1530080 = 191260 voxels = 295.9 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 600.30 voxels)

FEP_emo_vs_noemo





SPMresults: .\FEP_EMO_vs_NOemo

Height threshold T = 4.500480 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

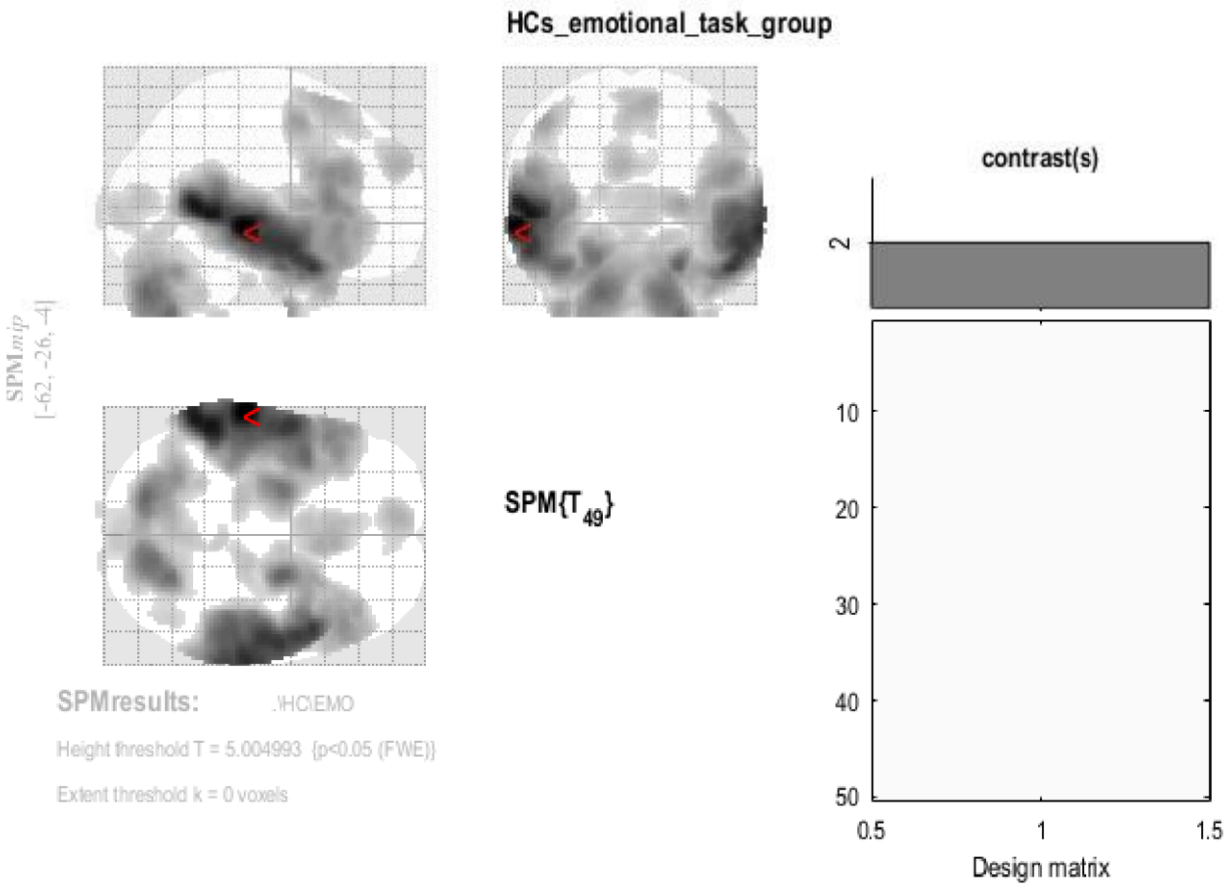
Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	
0.001	2	0.024	0.479	17	0.479	0.008	0.309	5.03	4.77	0.000	24 -8 -20
		0.024	0.479	18	0.465	0.023	0.446	4.73	4.52	0.000	50 -10 -22

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.50, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 35.747
Expected number of clusters, <c> = 0.05
FWEp: 4.500, FDRp: Inf, FWEc: 17, FDRc: Inf

Degrees of freedom = [1.0, 116.0]
FWHM = 20.3 19.3 19.3 mm mm mm; 10.2 9.6 9.6 {voxes}
Volume: 1524144 = 190518 voxels = 187.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 942.07 voxels)



Statistics: ***p-values adjusted for search volume***

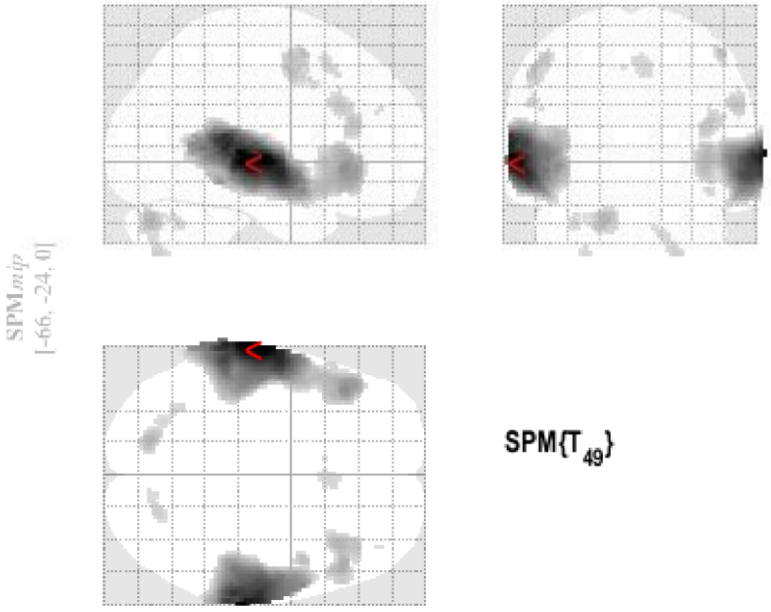
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*T*	($Z_{=}$)	p_{uncorr}			
0.000	7	0.000	0.000	14780	0.000	0.000	0.000	16.10	Inf	0.000	-62	-26	-4
						0.000	0.000	14.88	Inf	0.000	-56	-46	4
						0.000	0.000	14.66	Inf	0.000	-60	-54	8
		0.000	0.000	14499	0.000	0.000	0.000	13.63	Inf	0.000	68	-26	-6
						0.000	0.000	13.15	Inf	0.000	58	-10	-14
						0.000	0.000	13.01	Inf	0.000	52	10	-24
		0.000	0.000	9546	0.000	0.000	0.000	10.71	7.65	0.000	-18	-80	-38
						0.000	0.000	10.59	7.60	0.000	24	-68	-50
						0.000	0.000	10.49	7.56	0.000	16	-78	-40
		0.000	0.000	1256	0.000	0.000	0.001	7.54	6.12	0.000	6	14	62
						0.000	0.006	6.84	5.70	0.000	-4	26	54
						0.000	0.008	6.74	5.64	0.000	-4	8	66
		0.000	0.000	647	0.000	0.000	0.001	7.33	5.99	0.000	-6	56	28
		0.000	0.001	215	0.001	0.003	0.071	5.96	5.15	0.000	-16	-4	14
						0.021	0.464	5.31	4.69	0.000	-26	-2	6
						0.025	0.527	5.25	4.66	0.000	-12	-10	6
		0.006	0.113	40	0.113	0.005	0.109	5.81	5.04	0.000	-16	-26	-32

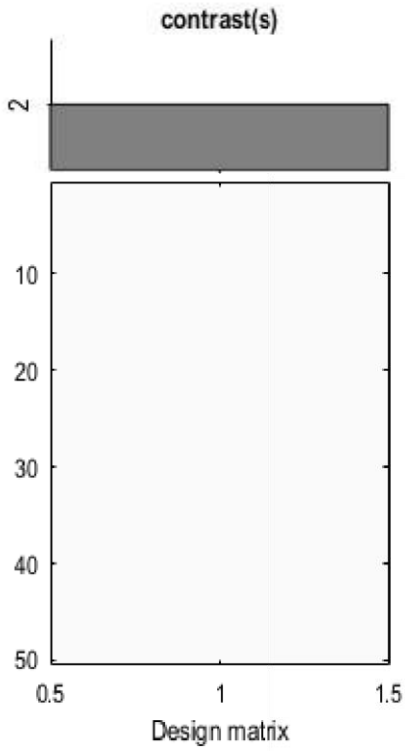
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 5.00, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 16.520
Expected number of clusters, <c> = 0.05
FWEp: 5.005, FDRp: 6.094, FWEc: 40, FDRc: 215

Degrees of freedom = [1.0, 49.0]
FWHM = 16.9 16.9 16.6 mm mm mm; 8.5 8.4 8.3 {voxels}
Volume: 1590800 = 198850 voxels = 311.6 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 594.03 voxels)

HCs_nonemotional_task_group





SPMresults: .\HC\NOEMO

Height threshold T = 5.096208 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*T*	($Z_{=}$)	p_{uncorr}			
0.000	17	0.000	0.000	4172	0.000	0.000	0.000	11.14	7.82	0.000	-66	-24	0
						0.000	0.000	11.09	7.80	0.000	-64	-16	0
						0.000	0.000	9.99	7.34	0.000	-66	-36	8
		0.000	0.000	2538	0.000	0.000	0.000	10.82	7.70	0.000	70	-28	2
						0.000	0.000	9.42	7.08	0.000	68	-24	-6
						0.000	0.000	9.36	7.06	0.000	68	-36	4
		0.000	0.000	460	0.000	0.001	0.046	6.42	5.44	0.000	50	26	2
						0.002	0.077	6.22	5.32	0.000	38	24	0
		0.000	0.008	138	0.002	0.002	0.077	6.23	5.32	0.000	-16	-76	-32
		0.011	0.328	17	0.213	0.003	0.127	6.01	5.18	0.000	48	4	54
		0.000	0.024	95	0.008	0.003	0.127	6.01	5.18	0.000	-54	-4	48
						0.009	0.265	5.69	4.96	0.000	-50	4	50
						0.019	0.517	5.43	4.78	0.000	-54	8	42
		0.000	0.024	92	0.008	0.006	0.202	5.84	5.06	0.000	40	32	18
		0.001	0.030	81	0.012	0.007	0.230	5.77	5.01	0.000	58	26	28
		0.002	0.085	51	0.040	0.012	0.344	5.60	4.90	0.000	22	-72	-50
						0.023	0.558	5.37	4.74	0.000	18	-76	-42
						0.030	0.655	5.28	4.67	0.000	12	-76	-36
		0.018	0.441	9	0.363	0.015	0.427	5.51	4.83	0.000	-56	20	28
		0.018	0.441	9	0.363	0.020	0.528	5.41	4.77	0.000	40	30	-16

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 5.10, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 11.727
Expected number of clusters, <c> = 0.05
FWEp: 5.096, FDRp: 6.417, FWEc: 1, FDRc: 81

Degrees of freedom = [1.0, 49.0]
FWHM = 15.0 15.2 15.6 mm mm mm; 7.5 7.6 7.8 {voxels}
Volume: 1569128 = 196141 voxels = 407.5 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 445.33 voxels)

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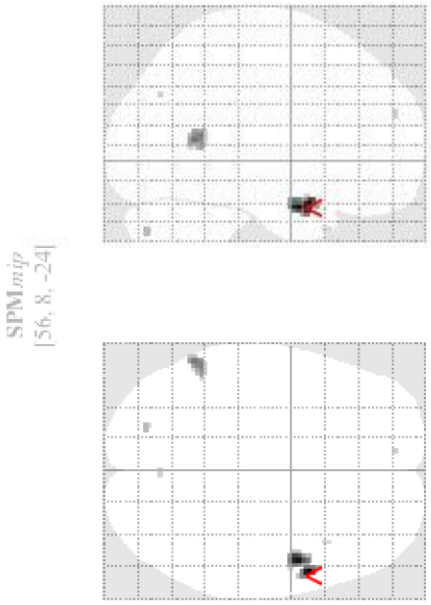
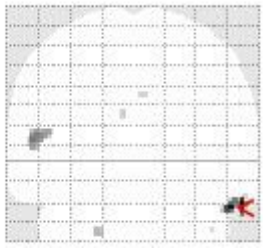
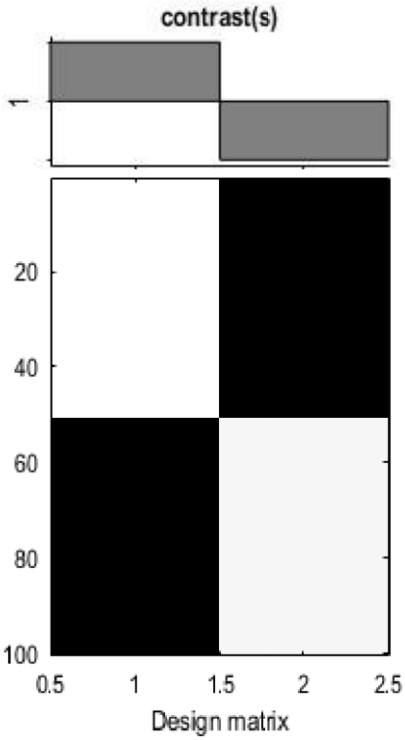
< >
1

HC_emo_vs_noemo





SPM{T_{98}}



SPMresults: .\HC_EMO_vs_NOemo

Height threshold T = 4.657810 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

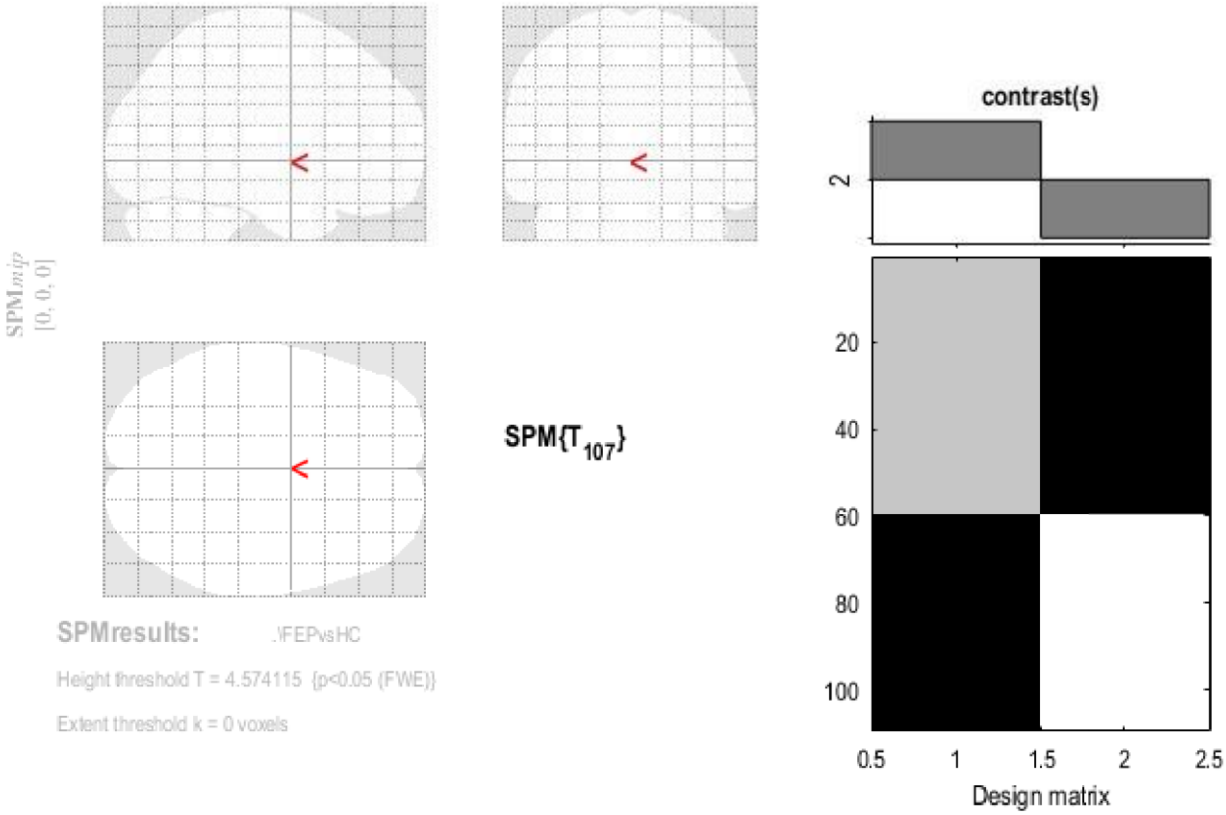
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*T*	($Z_{=}$)	p_{uncorr}			
0.000	6	0.004	0.341	71	0.071	0.002	0.210	5.59	5.20	0.000	56	8	-24
						0.003	0.210	5.48	5.10	0.000	50	2	-26
		0.006	0.341	53	0.114	0.012	0.516	5.08	4.78	0.000	-56	-54	10
		0.030	0.783	6	0.601	0.030	0.905	4.81	4.55	0.000	-20	-80	-40
		0.039	0.783	2	0.783	0.039	0.905	4.73	4.48	0.000	-8	54	24
		0.039	0.783	2	0.783	0.041	0.905	4.72	4.47	0.000	4	-72	34
		0.039	0.783	2	0.783	0.045	0.905	4.69	4.44	0.000	40	18	-38

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.66, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 21.977
Expected number of clusters, <c> = 0.05
FWEp: 4.658, FDRp: Inf, FWEc: 2, FDRc: Inf

Degrees of freedom = [1.0, 98.0]
FWHM = 17.4 17.2 17.2 mm mm mm; 8.7 8.6 8.6 {voxels}
Volume: 1564600 = 195575 voxels = 282.0 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 641.70 voxels)

Contrast_FEP_vs_HCs_emotional_task



SPMresults: .\FEPvsHC

Height threshold T = 4.574115 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	

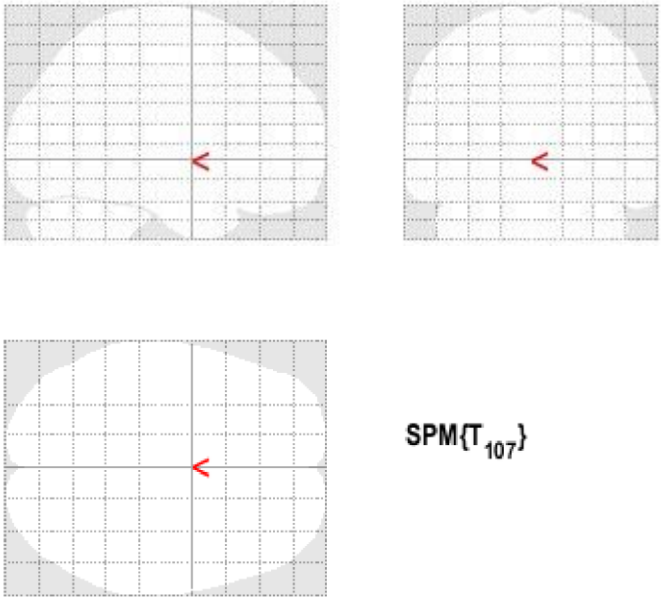
no suprathreshold clusters

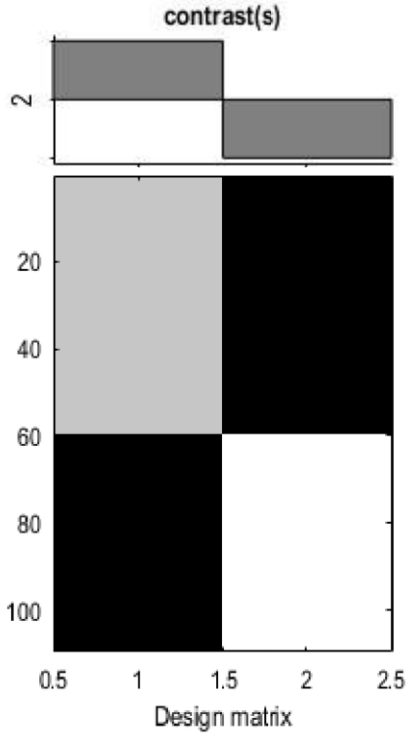
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.57, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 27.689
Expected number of clusters, <c> = 0.05
FWEp: 4.574, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 107.0]
FWHM = 18.8 18.3 17.9 mm mm mm; 9.4 9.1 8.9 {voxels}
Volume: 1510248 = 188781 voxels = 228.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 765.94 voxels)

Contrast_FEP_vs_HCs_emotional_task





SPMresults: .\FEPvsHC

Height threshold T = 3.168152 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	

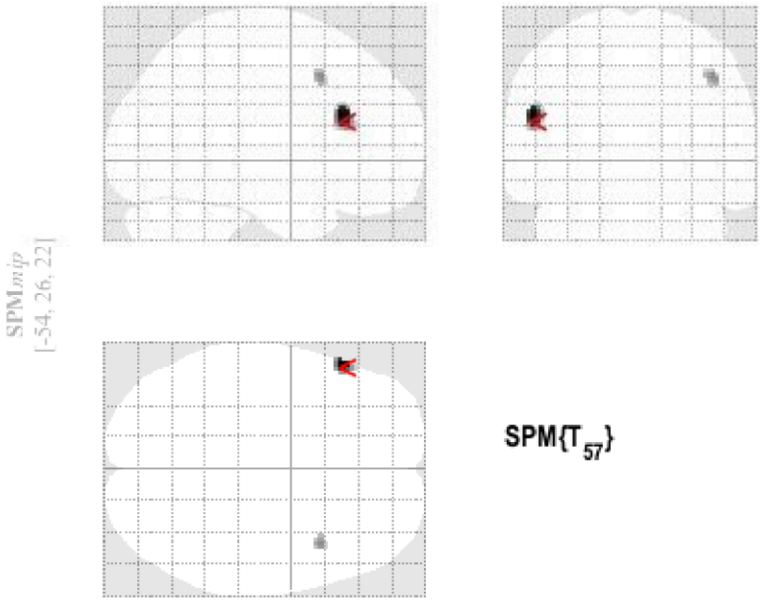
no suprathreshold clusters

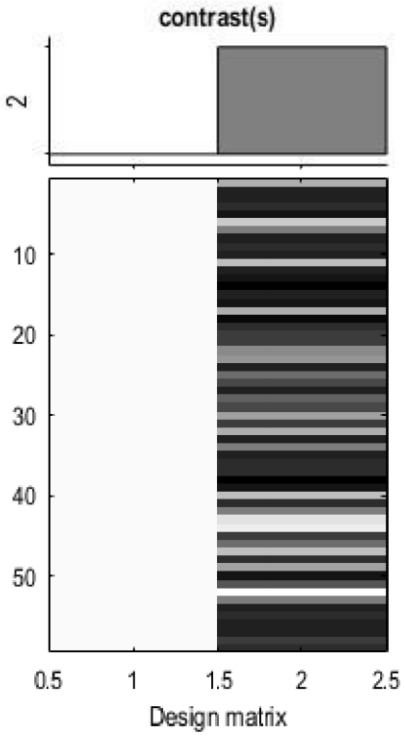
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.17, p = 0.001 (0.944)
Extent threshold: k = 0 voxels, p = 1.000 (0.944)
Expected voxels per cluster, <k> = 84.830
Expected number of clusters, <c> = 2.89
FWEp: 4.574, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 107.0]
FWHM = 18.8 18.3 17.9 mm mm mm; 9.4 9.1 8.9 {voxels}
Volume: 1510248 = 188781 voxels = 228.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 765.94 voxels)

Positive_Panss_correlation+_FEP_emo





SPMresults: .\4. Total_Positive_Panss_correlation

Height threshold T = 3.239478 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

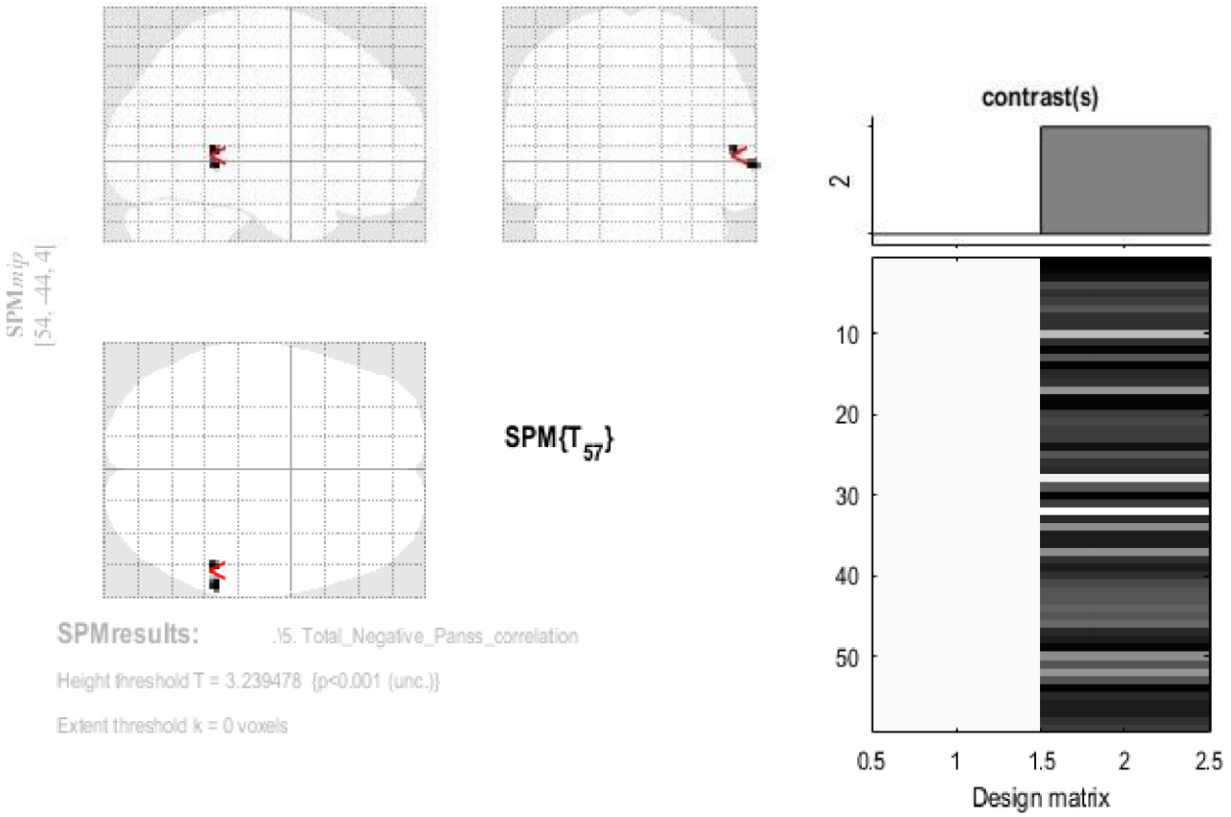
set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	
0.764	2	0.635	0.598	69	0.364	0.439	0.417	3.91	3.66	0.000	-54 26 22
		0.809	0.598	25	0.598	0.804	0.588	3.48	3.30	0.000	42 14 44

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.24, p = 0.001 (0.937)
Extent threshold: k = 0 voxels, p = 1.000 (0.937)
Expected voxels per cluster, <k> = 90.360
Expected number of clusters, <c> = 2.77
FWEp: 4.781, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 19.7 18.9 18.6 mm mm mm; 9.9 9.4 9.3 {voxels}
Volume: 1535184 = 191898 voxels = 205.7 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 866.83 voxels)

Negative_Panss_correlation+_FEP_emo



SPMresults: .\5. Total_Negative_Panss_correlation

Height threshold T = 3.239478 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

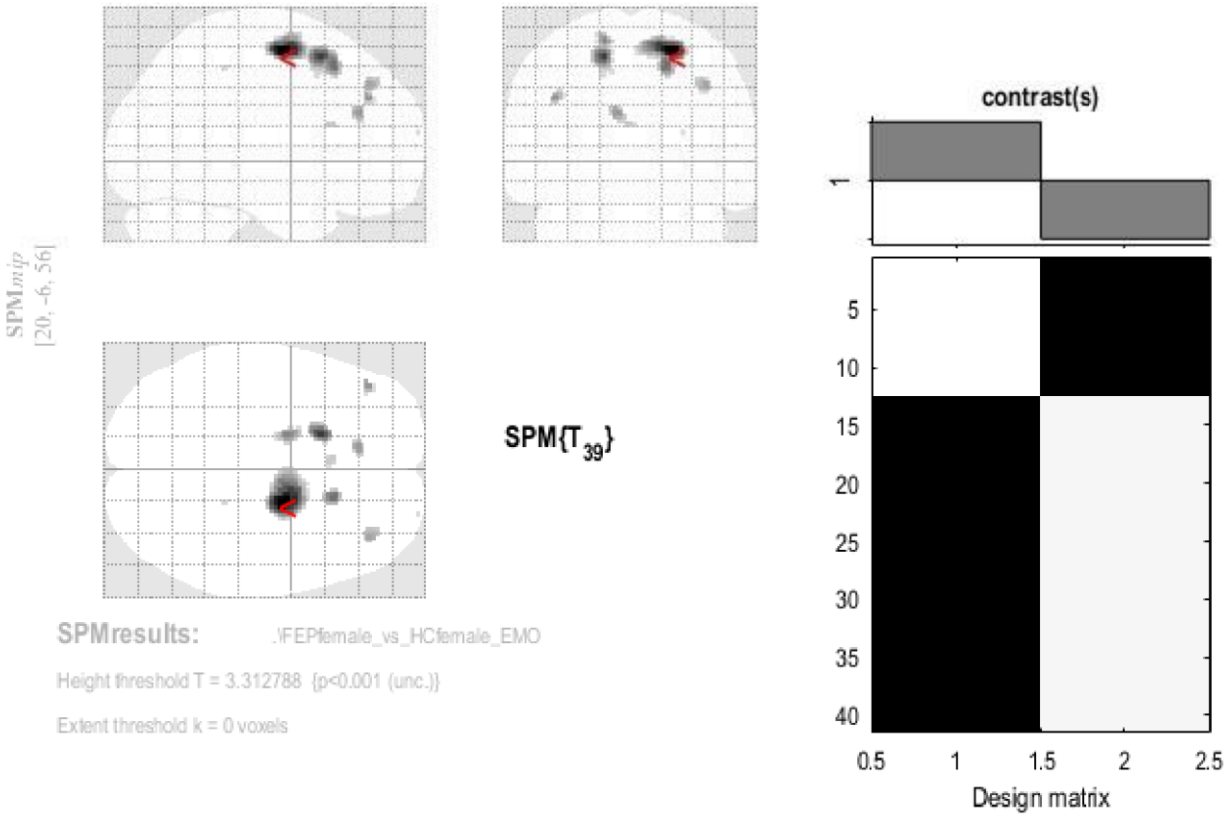
set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	
0.762	2	0.867	0.744	12	0.731	0.853	0.702	3.41	3.24	0.001	54 -44 4
		0.871	0.744	11	0.744	0.856	0.702	3.40	3.23	0.001	64 -42 -4

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.24, p = 0.001 (0.937)
Extent threshold: k = 0 voxels, p = 1.000 (0.937)
Expected voxels per cluster, <k> = 90.718
Expected number of clusters, <c> = 2.76
FWEp: 4.780, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 19.7 18.9 18.6 mm mm mm; 9.9 9.5 9.3 {voxels}
Volume: 1535184 = 191898 voxels = 204.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 870.26 voxels)

FEPfemale_vs_HCfemale_Emo



SPMresults: .\FEPfemale_vs_HCfemale_EMO

Height threshold T = 3.312788 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

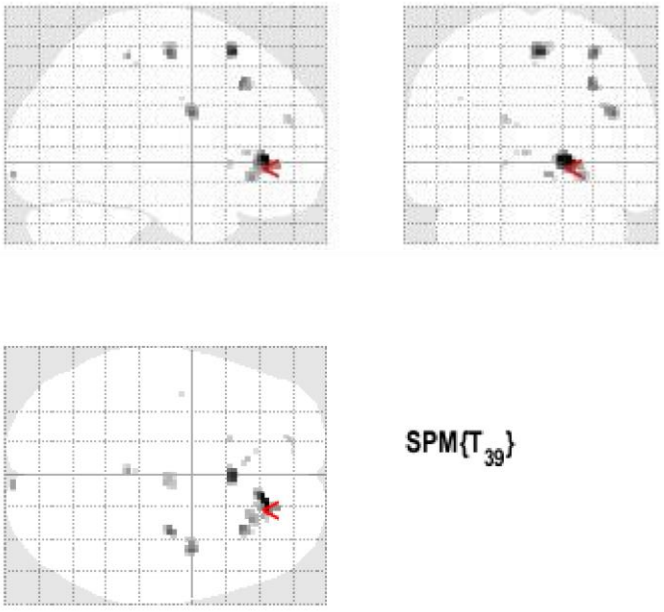
set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}			
0.002	10	0.079	0.245	399	0.025	0.096	0.211	4.84	4.25	0.000	20	-6	56
		0.516	0.928	106	0.216	0.267	0.323	4.39	3.93	0.000	-16	14	54
		0.683	0.928	62	0.342	0.492	0.522	4.06	3.68	0.000	18	20	50
		0.731	0.928	51	0.390	0.604	0.552	3.92	3.58	0.000	-16	-4	62
		0.891	0.934	15	0.660	0.700	0.589	3.80	3.49	0.000	-42	40	32
		0.846	0.928	25	0.557	0.724	0.589	3.77	3.46	0.000	-10	34	24
		0.846	0.928	25	0.557	0.789	0.589	3.69	3.39	0.000	38	40	40
		0.936	0.934	5	0.819	0.921	0.883	3.45	3.20	0.001	-2	18	18
		0.957	0.934	1	0.934	0.944	0.914	3.39	3.15	0.001	20	-38	48
		0.957	0.934	1	0.934	0.954	0.914	3.36	3.13	0.001	26	66	14

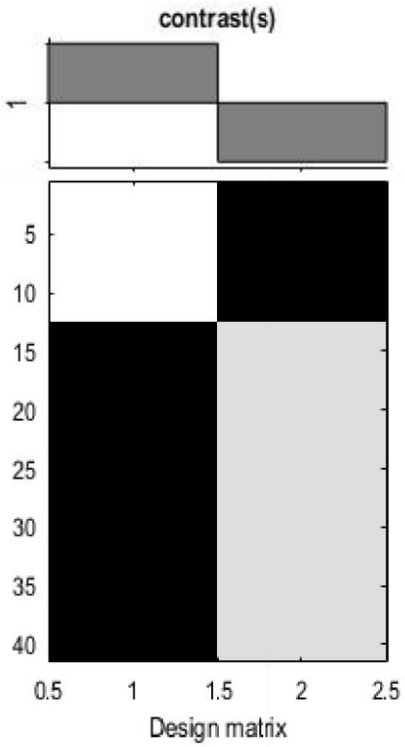
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.31, p = 0.001 (0.965)
Extent threshold: k = 0 voxels, p = 1.000 (0.965)
Expected voxels per cluster, <k> = 74.255
Expected number of clusters, <c> = 3.36
FWEp: 5.097, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 39.0]
FWHM = 18.6 18.2 17.9 mm mm mm; 9.3 9.1 9.0 {voxels}
Volume: 1568184 = 196023 voxels = 240.8 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 757.10 voxels)

FEPfemale_vs_HCfemale_Noemo





SPM*mip*
[18, 38, -2]

SPMresults: .\FEPfemale_vs_HCfemale_NOEMO

Height threshold T = 3.312788 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

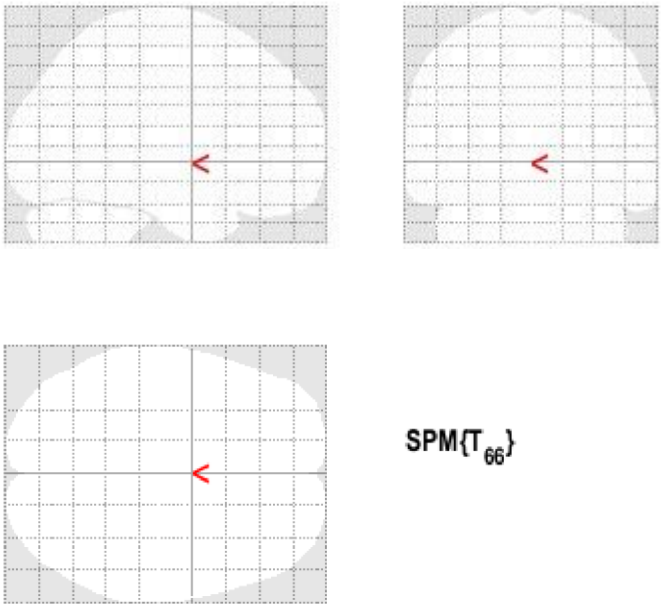
set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}			
0.000	16	0.603	0.909	78	0.174	0.641	0.985	4.08	3.70	0.000	18	38	-2
		0.904	0.909	25	0.441	0.778	0.985	3.91	3.57	0.000	2	20	56
		0.956	0.909	13	0.589	0.898	0.985	3.72	3.42	0.000	32	-14	56
		0.894	0.909	27	0.423	0.904	0.985	3.71	3.41	0.000	42	-2	24
		0.944	0.909	16	0.545	0.914	0.985	3.69	3.39	0.000	30	24	40
		0.952	0.909	14	0.574	0.954	0.985	3.58	3.31	0.000	26	30	-10
		0.982	0.909	5	0.756	0.965	0.985	3.54	3.28	0.001	0	-36	54
		0.987	0.909	3	0.819	0.969	0.985	3.53	3.26	0.001	8	-98	-8
		0.923	0.909	21	0.483	0.981	0.985	3.46	3.21	0.001	6	-16	56
		0.979	0.909	6	0.729	0.984	0.985	3.44	3.19	0.001	-16	50	22
		0.989	0.909	2	0.859	0.984	0.985	3.44	3.19	0.001	-6	28	4
		0.989	0.909	2	0.859	0.989	0.985	3.39	3.16	0.001	-16	18	-2
		0.992	0.909	1	0.909	0.994	0.985	3.33	3.10	0.001	-40	-8	32
		0.992	0.909	1	0.909	0.994	0.985	3.33	3.10	0.001	-10	52	18
		0.992	0.909	1	0.909	0.994	0.985	3.33	3.10	0.001	0	-32	50
		0.992	0.909	1	0.909	0.995	0.985	3.32	3.10	0.001	-10	32	4

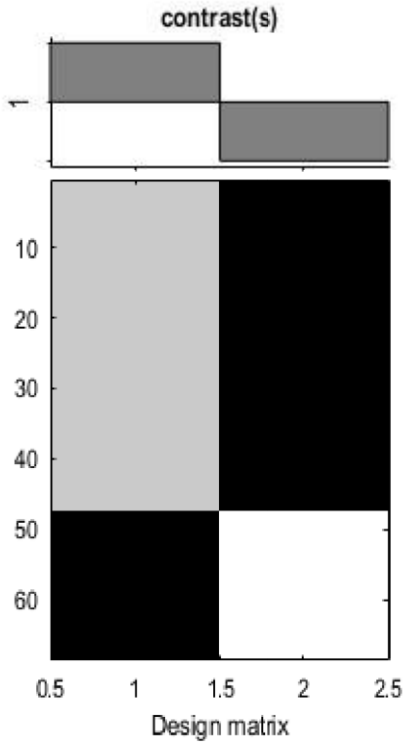
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.31, p = 0.001 (0.995)
Extent threshold: k = 0 voxels, p = 1.000 (0.995)
Expected voxels per cluster, <k> = 44.896
Expected number of clusters, <c> = 5.30
FWEp: 5.276, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 39.0]
FWHM = 15.2 15.3 15.8 mm mm mm; 7.6 7.6 7.9 {voxels}
Volume: 1557144 = 194643 voxels = 393.2 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 457.76 voxels)

FEPmale_vs_HCmale_emo





SPMresults: .\FEPmale_vs_HCmale_EMO

Height threshold T = 4.776012 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	

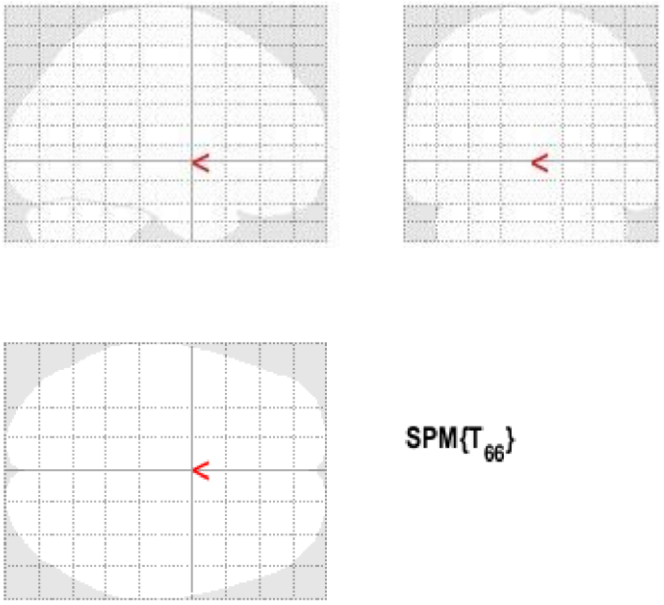
no suprathreshold clusters

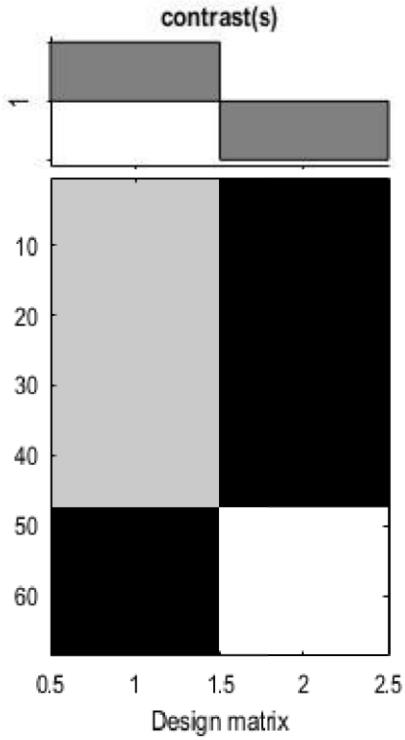
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.78, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 22.521
Expected number of clusters, <c> = 0.05
FWEp: 4.776, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 66.0]
FWHM = 18.3 17.7 17.5 mm mm mm; 9.1 8.8 8.7 {voxels}
Volume: 1561328 = 195166 voxels = 256.9 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 706.26 voxels)

FEPmale_vs_HCmale_emo





SPM{T_{66}}

SPMresults: .\FEPmale_vs_HCmale_EMO

Height threshold T = 3.218368 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	

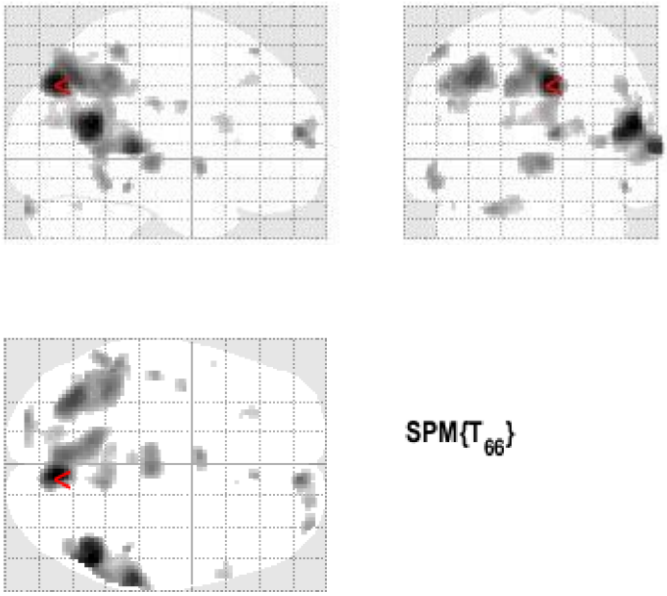
no suprathreshold clusters

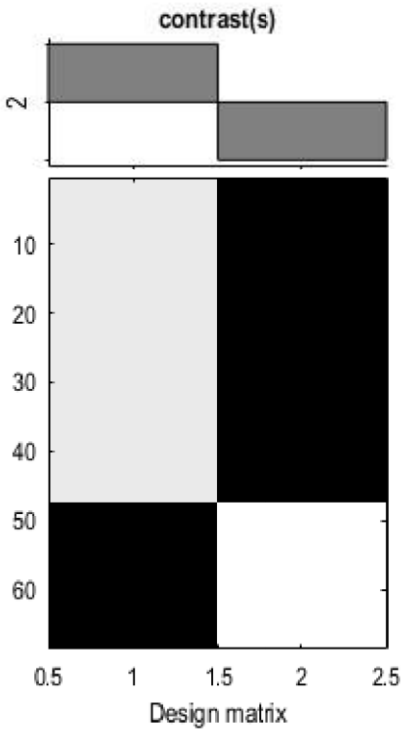
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.22, p = 0.001 (0.964)
Extent threshold: k = 0 voxels, p = 1.000 (0.964)
Expected voxels per cluster, <k> = 74.945
Expected number of clusters, <c> = 3.32
FWEp: 4.776, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 66.0]
FWHM = 18.3 17.7 17.5 mm mm mm; 9.1 8.8 8.7 {voxels}
Volume: 1561328 = 195166 voxels = 256.9 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 706.26 voxels)

FEPmale_vs_HCmale_nonemo





SPMresults: .\FEPmale_vs_HCmale_NOEMO

Height threshold T = 3.218368 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	*T*	($Z_=$)	p_{uncorr}			
0.000	22	0.001	0.004	1040	0.000	0.099	0.639	4.59	4.26	0.000	8	-74	40
						0.470	0.772	3.96	3.74	0.000	-2	-70	46
						0.553	0.772	3.87	3.66	0.000	-10	-56	40
		0.002	0.004	987	0.000	0.105	0.639	4.57	4.25	0.000	52	-56	16
						0.239	0.772	4.27	4.00	0.000	64	-32	4
						0.634	0.772	3.79	3.59	0.000	62	-50	4
		0.001	0.004	1083	0.000	0.329	0.772	4.13	3.88	0.000	-34	-64	42
						0.505	0.772	3.92	3.71	0.000	-38	-46	44
						0.620	0.772	3.80	3.60	0.000	-48	-44	38
		0.523	0.701	100	0.191	0.505	0.772	3.93	3.71	0.000	10	56	12
						0.869	0.837	3.50	3.34	0.000	24	60	16
		0.310	0.421	169	0.096	0.586	0.772	3.84	3.63	0.000	4	-24	-4
		0.813	0.862	36	0.433	0.683	0.772	3.74	3.54	0.000	-52	-42	56
		0.134	0.204	281	0.037	0.689	0.772	3.73	3.54	0.000	12	-48	34
						0.819	0.772	3.58	3.41	0.000	6	-48	26
						0.838	0.772	3.55	3.38	0.000	12	-46	14
		0.632	0.809	74	0.258	0.705	0.772	3.71	3.52	0.000	-22	-90	-28
						0.904	0.866	3.44	3.29	0.001	-12	-90	-24
		0.754	0.809	48	0.363	0.710	0.772	3.71	3.52	0.000	-2	2	-6
		0.702	0.809	59	0.312	0.734	0.772	3.68	3.50	0.000	-54	-50	-12

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.22, p = 0.001 (0.979)
Extent threshold: k = 0 voxels, p = 1.000 (0.979)
Expected voxels per cluster, <k> = 62.487
Expected number of clusters, <c> = 3.87
FWEp: 4.827, FDRp: Inf, FWEc: 987, FDRc: 987

Degrees of freedom = [1.0, 66.0]
FWHM = 17.5 16.6 16.2 mm mm mm; 8.7 8.3 8.1 {voxels}
Volume: 1541688 = 192711 voxels = 304.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 588.87 voxels)
Page 1

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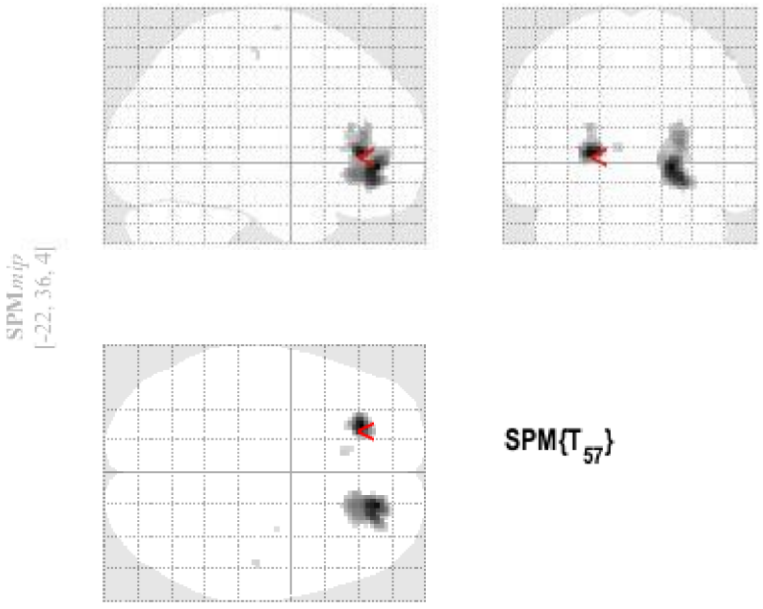
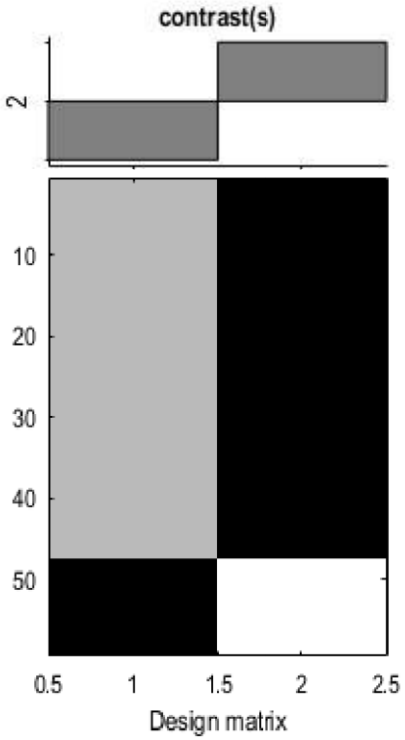
1

FEPmale_vs_FEPfemale_emo_hyperfemale





SPMresults: .\FEPmale_vs_FEPfemale_emo

Height threshold T = 3.239478 {p<0.001 (unc.)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

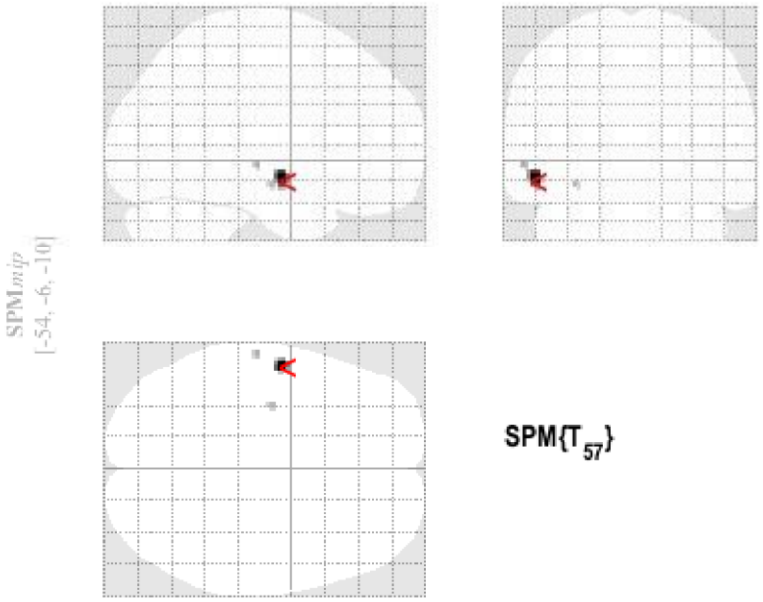
set-level		cluster-level				peak-level					mm mm mm		
p	*c*	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	*T*	$(Z_{=})$	p_{uncorr}			
0.198	5	0.413	0.434	140	0.173	0.014	0.042	5.25	4.72	0.000	-22	36	4
						0.753	0.751	3.59	3.40	0.000	-24	30	16
		0.046	0.077	515	0.015	0.026	0.042	5.04	4.57	0.000	20	44	-4
						0.285	0.351	4.16	3.87	0.000	20	32	-8
						0.351	0.351	4.06	3.79	0.000	24	36	10
		0.907	0.937	8	0.771	0.886	0.830	3.40	3.23	0.001	-8	26	6
		0.932	0.937	3	0.874	0.900	0.830	3.37	3.21	0.001	50	-20	56
		0.944	0.937	1	0.937	0.948	0.964	3.26	3.11	0.001	32	-10	70

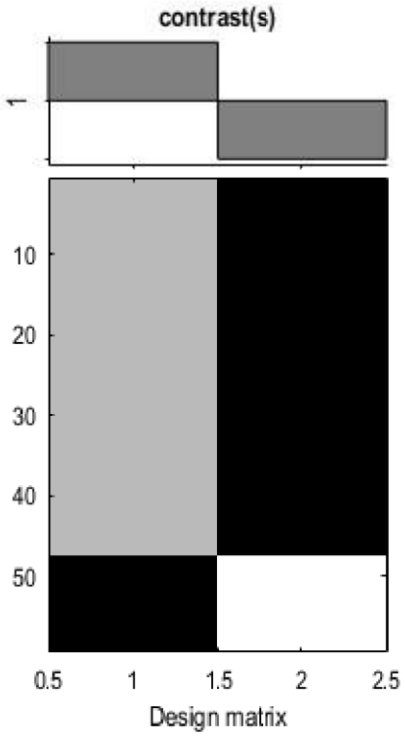
table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.24, p = 0.001 (0.954)
Extent threshold: k = 0 voxels, p = 1.000 (0.954)
Expected voxels per cluster, <k> = 80.273
Expected number of clusters, <c> = 3.08
FWEp: 4.818, FDRp: 5.044, FWEc: 515, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 18.9 18.1 18.0 mm mm mm; 9.4 9.1 9.0 {voxels}
Volume: 1532912 = 191614 voxels = 231.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 770.06 voxels)

FEPmale_vs_FEPfemale_emo





SPMresults: .\FEPmale_vs_FEPfemale_emo

Height threshold T = 4.817587 {p<0.05 (FWE)}

Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	$(Z_{=})$	p_{uncorr}	
0.000	3	0.011	0.633	35	0.211	0.006	0.359	5.51	4.91	0.000	-54 -6 -10
		0.033	0.693	5	0.654	0.032	0.720	4.97	4.51	0.000	-60 -20 -4
		0.035	0.693	4	0.693	0.036	0.720	4.93	4.48	0.000	-32 -12 -14

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.82, p = 0.000 (0.050)
Extent threshold: k = 0 voxels, p = 1.000 (0.050)
Expected voxels per cluster, <k> = 23.971
Expected number of clusters, <c> = 0.05
FWEp: 4.818, FDRp: Inf, FWEc: 4, FDRc: Inf

Degrees of freedom = [1.0, 57.0]
FWHM = 18.9 18.1 18.0 mm mm mm; 9.4 9.1 9.0 {voxels}
Volume: 1532912 = 191614 voxels = 231.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 770.06 voxels)