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Processing music in the first episode of major depressive disorder without treatment

Enrique Octavio Flores-Gutiérrez,[1] Juan José Cervantes,[1] Marina Torres Álvarez,[2] Sarael Alcauter Solórzano[3]

Original article

SUMMARY

The purpose of this study is the assessment of the differences in brain activity when patients with major depressive disorder (MDD) listen to two different types of music, with healthy subjects as control, by using functional Magnetic Resonance Imaging (fMRI). Brain activity with musical stimuli in healthy subjects has been investigated extensively, but there are few neurobiological music studies in mental illness, particularly in MDD. Studies in this area provide a new perspective on interdisciplinary research to explore the neurobiological substrates of MDD. This study involved 20 male subjects: 10 patients (34 ± 7 years), and 10 control subjects (33 ± 7 years). The MDD patients were selected in the pre-consultation service of the National Institute of Psychiatry Ramón de la Fuente Muñiz (INPRFM) of Mexico City, and control subjects were selected from workers of the Institute who responded to the invitation. All participants completed the Hamilton scales for anxiety and depression, Beck inventories for depression and anxiety, and the SCL-90-R. The Mini–Mental State Examination test was also administered to patients for diagnostic purposes. The fMRI was obtained by Philips Achieva 3-Tesla in the INPRF; analysis was made using the SPM2 format MRIcro system. The experimental stimuli were two pieces of music: one by JS Bach validated as tranquil and another one by J Prodromidès validated as disturbing. Results show differences between both groups of subjects and between types of music. In all cases, the parahippocampal area, the tail of the caudate nucleus and the auditory temporal cortex were activated. The neurobiological processing of music is affected by MDD. We discuss the clinical and cognitive implications of these findings.

Key words: Major depressive disorder, functional magnetic resonance imaging, music.

RESUMEN

El propósito de este estudio fue registrar diferencias durante la audición de dos tipos diferentes de música en pacientes con Trastorno Depresivo Mayor (TDM), comparados con sujetos sanos, mediante imagen por resonancia magnética funcional (IRMf). La actividad cerebral con estímulos musicales ha sido investigada ampliamente en sujetos sanos, pero son escasos los estudios del procesamiento de la música en estados de patología mental, particularmente en el TDM. Los estudios en esta área interdisciplinaria proveen una nueva perspectiva de investigación para explorar los sustratos neurobiológicos del TDM. Participaron 20 sujetos de sexo masculino: 10 pacientes con TDM (34 ± 7 años) y 10 sujetos control (33 ± 7 años). Los pacientes se seleccionaron en el servicio de pre-consulta del Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz (INPRFM) de la Ciudad de México, y los sujetos control entre los trabajadores del propio Instituto que respondieron a la invitación. Todos los participantes contestaron, con fines de confirmar el diagnóstico, las escalas de ansiedad y depresión de Hamilton, los inventarios de Beck para ansiedad y depresión y el SCL-90-R. A los pacientes se les aplicó además el MINI-mental test. Para la IRMf se usó un equipo Philips Achieva de tres Teslas en el INPRFM, el análisis se hizo con el formato SPM2 usando el sistema MRIcro. Los estímulos experimentales fueron una obra musical de JS Bach validada como tranquila y otra de J Prodromidès validada como inquietante. Los resultados muestran diferencias tanto entre los grupos de sujetos como entre los tipos de música: en todos los casos se activó el área parahipocampal, la cola del núcleo caudado y la corteza temporal auditiva. Concluimos que el procesamiento neurobiológico de la música es afectado por el TDM. Se discuten las implicaciones clínicas y cognoscitivas de estos hallazgos.

Palabras clave: Trastorno depresivo mayor, imagen por resonancia magnética funcional, música.

INTRODUCTION

MDD has serious repercussions on the quality of life and social functioning of affected patients. In Mexico, it has a rate of morbidity high enough to be a cause of significant levels of absence from work.[1,2] The World Health Organization reports that by 2020, depression could be the second greatest cause of deterioration in social and working function in the world. Furthermore, in recent years, the incidence of this disorder increased not only in adults, but also to an alarming extent, in children and young people.[3] In the face of these predictions, it is important to develop investi-

[1] Directorate of Clinical Research at the National Institute of Psychiatry Ramón de la Fuente Muñiz.
[2] Directorate of Clinical Services at the National Institute of Psychiatry Ramón de la Fuente Muñiz.
[3] Institute of Neurobiology, UNAM.

Correspondence: Enrique O. Flores-Gutiérrez. Clinical Research at the National Institute of Psychiatry Ramón de la Fuente Muñiz. Calz. México-Xochimilco 101, San Lorenzo Huipulco, Tlalpan, 14370 Mexico City. E.mail: florese@imp.edu.mx

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gations that contribute new knowledge about this disorder and strategies for treating affected patients.

The relationship between depressive disorder and music has its background in scientific literature and has been approached from the clinical perspective, although related publications are few. For example, Nielzén and Cesarec[4] compare patients with various psychological pathologies with control subjects (C/s) and find that the experience of music in depressed patients is less pleasurable than for the C/s and for other patients with different psychiatric diagnoses. Another recent study by Punkanen et al.[5] compares patients with depression with a group of C/s exposed to musical stimuli. These authors demonstrated a negative emotional slant in patients with depression and conclude that the assessment of musical emotions could be a pre-diagnostic method for deducing the presence of depression. One other study, carried out by Naranjo et al.,[6] confirms that the processing of emotional stimuli produced by music in MDD is associated with a "negative general slant" and concludes that the alteration of emotional processing is not confined to interpersonal stimuli (faces and voices), but is also manifested in the inability to experience music normally. Finally, Osuch et al.[7] made a study of cerebral imaging using fMRI in patients with depression, comparing them to C/s. When listening to pieces of music chosen by the participants themselves as their favorites in contrast to neutral pieces, responses were reported in the reward circuit of the C/s and significant deficits were reported in depressive patients. These works suggest that the response to musical stimuli can be useful in making affective, cognitive, and physiological assessments in real time, which could have possible applications in the prevention, diagnosis, treatment, and rehabilitation in the clinic, given that the stimuli are easily administered and the clinical support and neurobiological evidence for its efficacy is increasingly widespread.[6-8]

In the present study we propose that upon listening to music, the cerebral participation of the affective system in p/MDD compared to C/s will have appreciable differences with the fMRI technique. Stimuli were used that had opposite emotional effects in order to contrast their consequences in cerebral processing.

We recruited patients in their first episode and without previous treatment, given that neurophysiological changes and cognitive variables had been reported in recurring depression that were different to patients with a first episode.[9,10] Furthermore, patients with anti-depressive treatment or with previous consumption of other drugs can present important differences in studies of cerebral imaging compared to patients with no previous treatment.[11-13] Furthermore, in spite of MDD being twice as common in women than it is in men, we decided to carry out this project on male subjects only, given that women have periodic hormonal variations that can alter the perception of affective stimuli.[14]

METHOD

Subjects

Some 20 adult males between 21 and 45 years of age participated in this study, who were skilled and not musical. Ten were control subjects who were clinically healthy (33 ± 7 years) workers at the National Institute of Psychiatry Ramón de la Fuente Muñiz who responded to an invitation to participate, compared with patients via the pairing method. Ten others were patients with a primary diagnosis of MDD in their first episode and without treatment (34 ± 7 years), recruited via the pre-consultation Service of the Clinical Services of the same Institute, selected in accordance with the diagnostic criteria for major depressive disorder set out in the DSM-IV-TR. Furthermore, the participants had to meet the following conditions:

- *Patients*. Inclusion criteria: male, skilled, non-musical, aged between 21 and 45 years, with a diagnosis of major depressive disorder as per the DSM-IV and the MINI-mental Test with a score equal to or higher than 22 points on the Hamilton depression scale, and who have not received previous psychological pharmacological treatment. Exclusion criteria: unbalanced medical conditions, recent suicidal intent or ideas, serious depression with psychotic symptoms, co-morbidity with other psychiatric disorders, abuse of or dependency on addictive substances.
- *Control subjects*. Inclusion criteria: Skilled and non-musical males aged between 21 and 45 years, no present psychiatric diagnosis or previous psychiatric treatment received. Exclusion criteria: clinical evidence of unbalanced medical condition, history of suicidal ideas or intent, clinical evidence of abuse of or dependency on addictive substances. In all cases prior to the research protocol, the participants gave their informed consent, signing the respective letter (document prepared and approved by the INPRFM Ethics Committee in compliance with the Helsinki Declaration). After this, they were studied during a session of fMRI, where they listened to two pieces of music with no additional tasks.

General procedure

The neuro-imaging sessions were programmed within the three days following diagnosis. They were carried out in the cerebral imaging unit of the INPRFM. In order to carry out the session with musical stimuli, the participants were provided with non-magnetic earphones (Avotec Inc., Stuart, Fl, EU), and were put onto the sliding table built into the resonator. An experimental design was applied in blocks. The time within the scanner was approximately 30 minutes plus the time to acquire the anatomical references. The sessions had a maximum duration of 45 minutes.

Stimuli

During the fMRI sessions, two pieces of instrumental music were played, previously validated for their emotional effect.[8,15,16] One was an original contemporary piece of music by the composer Jean Prodromidès (1927–) for symphony orchestra, choir, and special instruments, that induces feelings of discomfort. It is an unpredictable and agitated piece, with dissonance and impactful effects, used in the soundtrack to the movie "Danton" by the filmmaker Pruszak in 1983. The other piece was "Invention" for three voices, BWN 797, by Johann Sebastian Bach, a soft and delicate piece originally written for the harpsichord and arranged for the piano by the pianist Glenn Gould, recorded in 1959. This work is characterized by its proven induction of feelings of tranquility. White noise taken from FM radio was also used as a control stimulus. The musical stimuli were prepared by using the free audio-recording and editing program Audacity (see http://audacity.sourceforge.net/?lang=es [28/01/13]). A passage of each piece of music was selected to complete a total duration of four minutes, which was divided into equal blocks of 24 seconds and interspersed with white noise in blocks of 24 seconds, which resulted in eight minutes of each type of music and white noise for each track. The stimuli were stored in a digital file and recorded onto a CD to reproduce the stimuli in a contra-balanced manner for all the sessions.

Functional magnetic resonance

The acquisition of cerebral imaging was carried out using the Philips Achieva 3.0 T (Philips Medical Systems, Eindhoven, Netherlands). During the presentation of each of the pieces of edited music, a series of echo planar images were obtained (EPI-SingleShot) on an axial orientation, weighted to T2* (TR=2000ms, TE=35ms), in 31 cuts of 4mm, voxel size of $3x3x4mm^3$, covering the total cerebral volume. As a high resolution anatomical reference and contrast, the acquisition of T1 images was included with inversion recovery (IR) pulses, TR=2949ms, TE=15ms, time of inversion (TI) 400ms, with the same localization and orientation as the functional images.

Image analysis

The data was transferred to a work station via the Philips scanner image format. The images were transferred and saved within the SPM2 analysis format as groups in time order, using the MRIcro system by Chris Rorden. They were statistically analyzed using SPM2 software (Wellcome Department of Imaging Neuroscience). The lineation was ensured using the standardized procedures included in SPM.[17] The images were softened using Gaussian blur with an FWHM of 6mm. The functional signs were obtained with correlation to box-car function and with convolution to the hemodynamic response function with no correction of derivative time.[17] The statistical analysis of the data was based on the General Lineal Model (GLM). *Clusters* composed of fewer than five voxels were excluded from the analysis. The significance of the maps of probability was calculated for each condition within the standardized space of Talairach.[18]

RESULTS

The image of the activated areas is summarized in Figure 1. The list of local maximums with a value of 1-p for each group of voxels corresponding to each condition is shown in Tables 1-4. The differences were evident between patients with MDD (p/MDD) and the C/s, and also between the works of Bach and Prodromidès (Figure 1). The p/MDD group presented the lowest number of activations for both types of music. In this sense, Bach's work was the least demanding, and both the C/s and the p/MDD showed the lowest number of activations (Tables 3 and 4). Indeed, they only had activity in the left caudate (tail) and in the right hemisphere in restricted areas of the hippocampus, the parahippocampus, and the fusiform gyrus. The latter two were active in all cases. In contrast, during the music by Prodromidès, all subjects employed a greater number of cerebral regions (Tables 1 and 2).

The basal ganglions had different activations during the work by Prodromidès: the bilateral caudate nucleus (body) in C/s only, whereas the putamen and the *globus pallidus* were activated in both the C/s and the p/MDD (Tables 1 and 2). The caudate nucleus (tail) was active in all conditions. The right *claustrum* only generated maximum activity in p/MDD while listening to the fragments by Prodromidès (Table 1). This work also required activity in the basal ganglions in p/MDD, as well as other structures (Table 3).

The anterior insular cortex had activation in C/s both for the tranquil as for the disturbing music, but in p/MDD there was none for either of the pieces of music (Tables 1

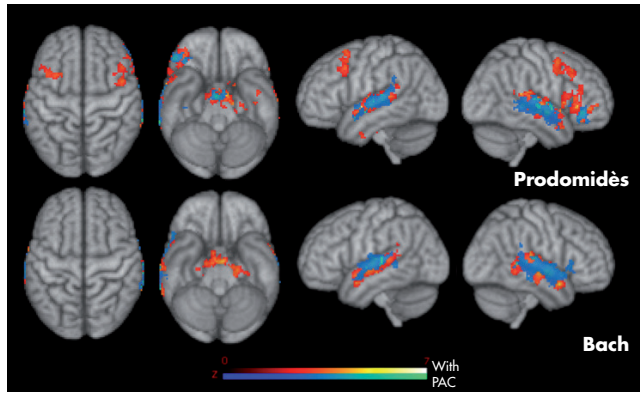

Figure 1. BOLD contrast in the groups, of MDD patients (blue-green) and control subjects (red-yellow), during the presentation of the disturbing music (*Prodomidès*) and the calm music (*Bach*).

Table 1. Anatomical localization of the areas activated in p/MDD on listening to the work of Prodromidès during the fMRI study

Patients/Prodromidès													
Left	BA	X	Y	Z	Range (mm)	Data attached	Right	BA	X	Y	Z	Range (mm)	Data attached
Hippocampus		-33	-31	-3	1	9	Medial Frontal Lobe	46	51	48	14	0	14
Sub-gyral Hippocampus	-33	-29	-5	2	9		Medial Frontal Lobe	47	40	35	-5	2	14
Sub-gyral Hippocampus	-31	-27	-5	2	9		Medial Frontal Lobe	47	46	39	-6	1	14
Sub-gyral Hippocampus	-28	-25	-7	0	4		Medial Frontal Lobe	47	33	35	-5	2	1
Tail of the caudate nucleus	-35	-30	-5	2	9		Inferior Frontal Lobe	47	53	36	-6	0	14
Tail of the caudate nucleus	-33	-33	-1	1	5		Inferior Frontal Lobe	47	50	36	-8	1	14
Superior Temporal Lobe	41	-43	-37	9	1	16	Inferior Frontal Lobe	47	47	37	-12	0	14
Superior Temporal Lobe	41	-51	-34	13	3	16	Claustrum		28	8	10	0	15
Superior Temporal Lobe	22	-61	-27	4	0	16	Sub-gyral Hippocampus		34	-30	-5	2	13
Superior Temporal Lobe	38	-50	4	-14	1	16	Sub-gyral Hippocampus		33	-28	-7	0	13
Medial Temporal Lobe	22	-62	-29	5	1	16	Sub-gyral Hippocampus		34	-26	-7	0	13
Medial Temporal Lobe	21	-54	-8	-9	3	16	Sub-gyral Hippocampus		32	-29	-5	1	13
							Sub-gyral Hippocampus		33	-31	-3	1	13
							Sub-gyral Hippocampus		25	-44	5	3	12
							Sub-gyral Hippocampus		23	-41	7	4	12
							Thalamus		13	-4	6	0	15
							Thalamus		3	-8	-3	3	15
							Pulvinar Thalamus		12	-29	17	2	10
							Pulvinar Thalamus		13	-31	15	2	10
							Pulvinar Thalamus		16	-31	15	2	10
							Pulvinar Thalamus		18	-33	13	1	8
							Pulvinar Thalamus		18	-35	11	2	6
							Pulvinar Thalamus		14	-25	19	2	2
							Tail of the caudate nucleus		33	-31	-1	1	13
							Tail of the caudate nucleus		21	-39	9	3	7
							Lentiform Nucleus		13	-2	6	1	15
							Putamen		26	6	10	1	15
							Putamen		25	-9	11	0	11
							Putamen		26	-10	6	0	11
							Putamen		27	8	8	0	15
							Superior Temporal Lobe	42	67	-11	6	0	17
							Superior Temporal Lobe	22	67	-10	4	1	17
							Superior Temporal Lobe	22	61	1	-3	1	17
							Superior Temporal Lobe	22	69	-38	5	1	17
							Medial Temporal Lobe	22	70	-36	3	2	17
							Medial Temporal Lobe	22	73	-35	2	4	17
							Fusiform	20	45	-11	-23	1	3

BA = Areas of Brodmann; X, Y, Z = Coordinates of Talairach: X ([–] left; [+] right), Y ([–] posterior; [+] anterior), Z ([–] inferior; [+] superior) (Lancaster et al., 2000). Radius of the "Clusters" ≥ 5 voxels; "Family Wise Error" corrected p = 0.05 (Friston et al., 1995).

and 3 - 2 and 4).

The posterior parahippocampal cortex only had activations during the work by Bach, bilaterally in C/s and on the right in p/MDD. The work by Bach did not require frontal activity in either group (tables 3 and 4). In contrast, the work by Prodromidès did demand abundant frontal bilateral activity in the C/s and on the right in the p/MDD (Tables 3 and 4).

DISCUSSION

This study compares the cerebral metabolic response of male patients with major depressive disorder in their first episode and with no prior treatment with control subjects, with the sole task of listening to two types of music unknown to the participants (one tranquil and one disturbing). We confirm the hypothesis that the p/MDD had hypofunction in areas related to the neuro-cognitive processing of music, as opposed to the C/s who showed activity cerebral areas typical for this type of stimulus.[19-21]

Comparison with other publications

There are few works which relate MDD with the experience of music; we found only three behavioral studies and only one that applied the fMRI technique. The behavioral studies are those by Nielzèn,[4] Punkanen[5] and Naranjo.[6] The principle findings of these studies were firstly, as in our study, that the patients with depression showed less reactivity to music; and secondly, a negative slant to the emotions was

Table 2. Anatomical localization of the areas activated in C/s on listening to the work of Prodromidès during the fMRI study

Controls/Prodromidès													
Left	BA	X	Y	Z	Range (mm)	Data attached	Right	BA	X	Y	Z	Range (mm)	Data attached
Superior Frontal Lobe	8	-43	17	55	3	8	Medial Frontal Lobe	6	42	8	54	0	26
Medial Frontal Lobe	6	-25	16	58	1	25	Medial Frontal Lobe	6	33	17	63	5	18
Medial Frontal Lobe	6	-27	15	58	1	25	Medial Frontal Lobe	6	35	15	62	4	18
Medial Frontal Lobe	8	-43	27	49	2	15	Medial Frontal Lobe	6	45	7	52	1	26
Medial Frontal Lobe	8	-47	29	41	1	7	Medial Frontal Lobe	6	44	12	52	0	26
Precentral Frontal Lobe	9	-38	16	35	0	25	Medial Frontal Lobe	8	55	17	41	1	6
Precentral Frontal Lobe	9	-43	18	34	0	25	Medial Frontal Lobe	8	55	15	41	0	5
Precentral Frontal Lobe	9	-42	19	40	3	25	Medial Frontal Lobe	8	36	16	45	2	26
Precentral Frontal Lobe	9	-40	16	40	3	25	Medial Frontal Lobe	9	47	7	38	1	26
Postcentral	40	-67	-20	16	2	9	Medial Frontal Lobe	11	41	36	-14	1	27
Anterior Cingulate	32	-10	22	38	0	21	Medial Frontal Lobe	47	41	36	-10	1	27
Anterior Cingulate	32	-13	23	37	0	21	Inferior Frontal Lobe	10	40	46	-2	2	27
Anterior Cingulate	32	-13	19	39	2	21	Inferior Frontal Lobe	46	37	35	12	0	27
Anterior Cingulate	32	-21	7	45	1	19	Inferior Frontal Lobe	47	42	31	0	5	27
Sub-Gyral	32	-11	23	40	0	21	Precentral	9	40	23	36	0	26
Insula	13	-31	-30	17	1	28	Thalamus		21	-20	13	0	11
Insula	13	-33	-19	21	0	12	Body of the caudate		13	-4	25	4	13
Thalamus		-7	-4	3	0	29	Posterior Cingulate	23	9	-29	27	2	10
Thalamus		-7	-3	1	2	29	Superior Temporal Lobe	42	70	-21	11	1	30
Thalamus		-3	-4	3	1	29	Superior Temporal Lobe	42	70	-23	12	1	30
Tail of the caudate nucleus		-37	-31	-7	3	24	Superior Temporal Lobe	22	67	-1	2	1	30
Tail of the caudate nucleus		-31	-35	1	2	3	Superior Temporal Lobe	22	61	-1	2	0	30
Body of the caudate		-19	7	21	4	20	Superior Temporal Lobe	22	61	-2	4	1	30
Body of the caudate		-17	7	21	2	20	Superior Temporal Lobe	22	65	-1	5	0	30
Body of the caudate		-18	-1	17	4	4	Superior Temporal Lobe	22	69	-47	18	1	16
Lentiform Nucleus		-6	-2	-1	2	29	Superior Temporal Lobe	22	69	-44	16	1	16
Putamen		-17	7	-5	0	29	Superior Temporal Lobe	22	68	-43	10	0	23
Parahippocampal	34	-10	-6	-17	3	29	Superior Temporal Lobe	22	71	-36	9	2	23
Sub-Gyral Hippocampus		-34	-28	-8	1	24	Medial Temporal Lobe	22	73	-35	3	4	23
Sub-Gyral Hippocampus		-35	-31	-7	3	24	Medial Temporal Lobe	22	67	-42	5	0	23
Transverse Temporal Lobe	41	-37	-34	13	0	28	Medial Temporal Lobe	22	69	-41	4	1	23
Transverse Temporal Lobe	42	-61	-11	8	2	28	Medial Temporal Lobe	21	71	-35	-5	3	2
Superior Temporal Lobe	22	-67	-12	1	2	28	Medial Temporal Lobe	21	71	-41	-13	4	1
Superior Temporal Lobe	22	-52	-3	-3	1	28	Medial Temporal Lobe	21	71	-19	-13	3	17
Superior Temporal Lobe	22	-69	-19	1	1	28	Medial Temporal Lobe	21	69	-43	-15	5	14
Medial Temporal Lobe	21	-44	-2	-29	0	22	Medial Temporal Lobe	21	70	-37	3	2	23
Inferior Temporal Lobe	20	-43	-14	-27	1	24							
Inferior Temporal Lobe	20	-46	-4	-37	3	22							
Inferior Temporal Lobe	20	-46	-3	-35	1	22							
Inferior Temporal Lobe	20	-45	-6	-28	1	22							
Inferior Temporal Lobe	20	-45	-4	-29	0	22							
Inferior Temporal Lobe	20	-44	-8	-29	1	22							
Fusiform	20	-42	-12	-25	1	24							
Fusiform	20	-42	-13	-23	0	24							

BA = Areas of Brodmann; X, Y, Z = Coordinates of Talairach: X ([–] left; [+] right), Y ([–] posterior; [+] anterior), Z ([–] inferior; [+] superior) (Lancaster et al., 2000). Radius of the "Clusters" ≥ 5 voxels; "Family Wise Error" corrected p = 0.05 (Friston et al., 1995).

confirmed in patients with MDD as well as the recognition of interpersonal stimuli that also affected the manner in which music is perceived. Our work is in accordance with these reports, and we know that the hypoactivity of the ventral striatum, evident in our p/MDD, can lead to a reduction of pleasure in the musical experience, expressed as little emotional reactivity and indifference. On the other hand, the frontal-striatal circuit, which has been related with musical anticipation[22] and the pleasure circuit,[23] seems essential in the gratifying function to give feeling to listening to music.[24] In terms of the slant towards negative thoughts and emotions present in depressed patients,[25,26] this can correspond to the excess activation of the *Default Mode Network* (DMN)[27] which has already been reported as hyperactive in patients with depression.[28-30] In the DMN, the posterior cingulate cortex has been proposed as responsible for self-referring thoughts with a negative slant.[30] Our results are in line with the proposal of the effect of cognitive and affective inter-

Table 3. Anatomical localization of the areas activated in p/MDD on listening to the work of Bach during the fMRI study

Patients/Bach													
Left	BA	X	Y	Z	Range (mm)	Data attached	Right	BA	X	Y	Z	Range (mm)	Data attached
Tail of the caudate nucleus		-37	-31	-7	3	8	Parahippocampal	28	26	-23	-10	2	7
Tail of the caudate nucleus		-35	-29	-5	1	8	Sub-gyral Hippocampus		27	-24	-8	3	7
Superior Temporal Lobe	42	-64	-26	9	1	9	Sub-gyral Hippocampus		29	-25	-5	2	7
Superior Temporal Lobe	41	-43	-36	3	3	5	Superior Temporal Lobe	42	71	-29	19	3	6
Superior Temporal Lobe	22	-61	-25	7	2	9	Superior Temporal Lobe	42	68	-28	7	0	10
Superior Temporal Lobe	22	-53	-12	-2	0	9	Superior Temporal Lobe	42	67	-28	9	0	10
Superior Temporal Lobe	22	-59	-26	6	1	9	Superior Temporal Lobe	22	68	-40	7	0	10
Medial Temporal Lobe	22	-55	-34	6	1	9	Superior Temporal Lobe	22	66	-40	7	1	10
Medial Temporal Lobe	21	-55	-19	-2	2	9	Medial Temporal Lobe	21	71	-25	-5	3	10
							Medial Temporal Lobe	21	63	4	-9	1	10
							Medial Temporal Lobe	21	71	-30	-10	3	4
							Fusiform	20	41	-9	-23	1	2
							Fusiform	20	45	-11	-23	1	1
							Sub-Gyral	20	43	-13	-21	1	3

BA = Areas of Brodmann; X, Y, Z = Coordinates of Talairach: X ([–] left; [+] right), Y ([–] posterior; [+] anterior), Z ([–] inferior; [+] superior) (Lancaster et al., 2000). Radius of the "Clusters" ≥ 5 voxels; "Family Wise Error" corrected p = 0.05 (Friston et al., 1995).

ference produced by the DMN.[29,31] In our p/MDD, the images showed an absence or reduction of activity in medial, striatal, limbic and para-limbic structures while listening to music.

Finally, the study by Osuch[7] contrasted listening to different types of favorite music with neutral music in depressed patients and control subjects using the fMRI technique. The proposal was to investigate the activation of the reward circuit. Activation was found in the circuit in the control subjects, but this was not the case in patients with depression, in whom the left parahippocampal gyrus was only found to be correlated with the pleasant music. Our

Table 4. Anatomical localization of the areas activated in C/s on listening to the work of Bach during the fMRI study

Controls/Bach													
Left	BA	X	Y	Z	Range (mm)	Data attached	Right	BA	X	Y	Z	Range (mm)	Data attached
Insula	13	-53	-38	15	3	11	Insula	13	39	-22	-9	3	6
Parahippocampal area	30	-18	-37	4	1	10	Parahippocampal area	19	31	-41	-5	1	9
Parahippocampal area	28	-16	-20	-17	3	10	Parahippocampal area	37	34	-43	-8	0	9
Thalamus		-3	-10	-3	3	10	Parahippocampal area	36	39	-33	-7	4	8
Thalamus		-1	-9	0	2	10	Parahippocampal area	36	39	-21	-11	4	2
Sub-Gyral		-3	-41	-3	2	10	Parahippocampal area	36	41	-21	-13	2	1
Superior Temporal Lobe	41	-35	-34	8	2	11	Thalamus		1	-9	-1	2	10
Superior Temporal Lobe	22	-50	-29	8	1	11	Tail of the caudate nucleus		37	-33	-4	2	8
Superior Temporal Lobe	22	-57	-35	-2	1	11	Posterior Cingulate	29	8	-41	10	2	7
Superior Temporal Lobe	22	-53	-10	11	2	11	Posterior Cingulate	29	5	-41	10	3	7
Medial Temporal Lobe	21	-50	-38	-2	1	11	Transverse Temporal Lobe	42	68	-17	11	1	12
Cerebellar Lingual		-55	-21	-7	0	4	Superior Temporal Lobe	41	57	-26	12	1	12
							Superior Temporal Lobe	22	56	-11	0	1	12
							Superior Temporal Lobe	42	59	-26	14	0	12
							Superior Temporal Lobe	38	50	9	-20	0	12
							Medial Temporal Lobe	21	50	1	-10	1	12
							Medial Temporal Lobe	21	73	-35	-5	4	5
							Medial Temporal Lobe	21	67	-1	-11	1	3
							Fusiform	37	40	-44	-11	2	9
							Fusiform	37	42	-44	-11	4	9
							Fusiform	37	43	-42	-13	2	9
							Fusiform	37	37	-44	-10	1	9

BA = Areas of Brodmann; X, Y, Z = Coordinates of Talairach: X ([–] left; [+] right), Y ([–] posterior; [+] anterior), Z ([–] inferior; [+] superior) (Lancaster et al., 2000). Radius of the "Clusters" ≥ 5 voxels; "Family Wise Error" corrected p = 0.05 (Friston et al., 1995).

results coincide in terms of the low response of regions activated in the p/MDD as opposed to the controls, but we also found the same phenomenon in the parahippocampal gyrus in the p/MDD with the pleasant music, in the right hemisphere (BA 28) only. The parahippocampal gyrus has already been related with listening to music; some investigations implicate it in a key contribution towards tasks of memory recovery and learning, particularly in contextual memory and also in the processing of new things.[32,33] It is possible that the difference of hemispheric lateralization between the Osuch[7] report and ours is such because they used pieces of music that were very familiar and favorites of each subject, and as such the processing was predominantly in the left hemisphere. In contrast, in our study the pieces were new and unknown to the participants and possibly because of this, they produced processing that was predominated by the right front-temporal lobe, as has already been reported in other studies.[34]

Differences between patients and controls

In the comparison of the two types of music, all subjects employed a greater number of cerebral regions listening to the work by Prodromidès. This effect has been previously reported[16] and possibly implies a more abundant neuronal incorporation in the pursuit of meaning for a work of structure and a form that is unorthodox, energetic, and unpredictable. In contrast, in the work of Bach, all subjects showed a lower number of activations, possibly as an economic response to a familiar stimulus with a predictable structure and from whose substrate the neuronal networks are pre-established by learning or implicit knowledge.[35-37] Some authors consider that this would be a phenomenon of enculturation, due to exposure to a tonal musical language from infancy that incorporates musical rules (grammar, syntax etc) which become as familiar as the native language.[38] In this way the listener, familiarized with such forms, develops expectations of musical happenings and a facilitation for the sequences that are generated from moment to moment.[36,39-41]

Other activated regions

The work by Prodromidès generated activity in the right *claustrum* of patients with MDD. This slim laminar structure, located between the putamen and the insular lobe, has multimodal neurons with distinct connections, whose function, as far as is known, is to coordinate cortical motor regions with the acquisition of sensory information in the perceptual recognition of the environment around us, possibly in order to synchronize actions related to spatial orientation and directed attention.[42] In the experience of music, and sound in general, the synchronization of events, spatial orientation, and directed attention are particularly important, both for processing the meaning of the sound as for the subsequent motor execution. Furthermore, it has been observed that the activity of the *claustrum* is required in situations relevant to self-preservation. The music of Prodromidès achieves a stimulation that generates stress with aggressive and threatening sounds that provoke survival responses with psychomotor tendencies towards action, which would necessarily imply said structure.[42-45]

In the C/s, the anterior insular was activated both for the pleasant as well as the unpleasant music, but in the p/MDD the insular did not appear activated for either of the pieces played. This is in line with some publications that report a diminished response in the anterior insular lobe in patients with unipolar depression.[46-48] On the other hand, the insula has also been related to social emotions[49] and with the multimodal paralimbic processing function.[50] In the experience of music it has been related to grammatical, emotional, cognitive, and rhythmic processing.[51-53] In our work we found that in contrast to the C/s, the anterior insular lobe did not show activity in the p/MDD. It is possible that the reduction or absence of striatal, limbic, and hypothalamic activity in p/MDD has a possible visceral repercussion that diminishes the information on the interoceptive emotional feedback of the insula itself.

Finally, the basal ganglions also had activation differences: the tail of the caudate nucleus was present in all cases, and the body of the caudate nucleus only in the C/s during the work by Prodromidès which also activated the putamen in the C/s and the p/MDD. We know that the basal ganglions are essential in the expression of correct schemes of action and in the appropriate selection of motor responses, including those of emotional and social states. These processes are fundamental for all goal-directed action.[54] In our study, these activations in the participants on hearing the music, primarily in the tail of the caudate nucleus, tell us about an intention or an action, from marking time using a finger or tapping a foot, to wanting to distance oneself from (or turn off) the disturbing music. The tail of the caudate nucleus has a close relationship with the amygdala functions and has a notable influence in the other structures of the basal ganglions.54 It also receives connections with temporal-parietal areas and, indirectly, the frontal cortex.[55,56] Furthermore, it has been related with cognitive function such as learning and planning behaviours.[57,58] Given that the pieces were not controlled by the participants, it is possible that in the tail of the caudate nucleus there has also been activity recorded as part of the learning experience.[57]

CONCLUSION

Our results show differences related to the type of music and the type of participant (depressive patient of control subject). In all cases, the superior and medial temporal gyrus was activated due to sensory auditory processing, as

well as the fusiform gyrus, parahippocampal regions, and the caudate nucleus (tail), which had activation in all conditions. The greater cortical demand that included frontal regions was recorded in the C/s with the disturbing music. The group of p/MDD presented the lowest number of activated cerebral regions for both types of music and more for the work validated as tranquil, which could be interpreted as minimal musical processing, in the conditions of alteration by the MDD of this study. The results in the p/MDD are also congruent with other reports that show hypofunction in the frontal cortex, basal ganglions, the limbic system, and other paralimbic zones.[59-62] New research is necessary in order to broaden the experimentation with music, given that it can provide relevant information on MDD.

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