Neuroanatomical basis of anxiety disorders in schizophrenia

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Introduction

Schizophrenia is a heterogeneous and severe psychiatric disorder. Additionally, it is known that a large group of schizophrenic patients have important comorbidity with anxiety symptoms (1, 2). However, it is still nuclear if there is a single neural deficit underlying the association between both conditions, that results in determined symptoms (3, 4). Therefore, our study aims to determine whether there is a neuroanatomical basis for the presence of both schizophrenia and anxiety symptoms.

Methods

Subjects

MRI datasets were acquired for 20 Schizophrenic-Anxious (SQZ/ANX) patients, 20 Schizophrenic (SQZ) patients, 20 Anxious (ANX) and 20 healthy Controls (Ctrl), matched by age, gender and handedness. The diagnosis of schizophrenia and anxiety was performed by trained clinical investigators based on the DSM-IV criteria and the Structured Clinical Interview for DSM-IV (SCID). Patients with co-morbidity for DSM-IV axis I or axis II disorders were not included, except for the SQZ/ANX patients, whom meet criteria for both conditions. For patients that were medicated at the time of the MRI scan, medications' types and doses were recorded and converted into chlorpromazine-equivalents (CPZ-eq). Clinical data of all subjects are shown in Table 1.

Table 1. Sociodemographic and Clinical Data

	SQZ/ANX n=20		SQZ n=20		ANX n=20		Ctrl n=20		*H*	*p*
	M	SD	M	SD	M	SD	M	SD		
Gender M/F	12/8		11/9		5/15		12/8			
Age	32.55	6.901	35.39	10.733	30.90	6.639	33.20	6.613	1.43	0.69
PANSS Positive	13.52	5.74	12.25	3.66	-	-	-	-	0.44	0.50
PANSS Negative	18.52	7.82	15.50	5.29	-	-	-	-	1.17	0.27
PANSS Total	65.58	21.41	59.35	16.40	-	-	-	-	0.45	0.50
Medication	239,31	196.12	285.62	187.02	-	-	-	-	0.05	0.81
K-Bit	95.65	11.03	91.05	13.76	103.65	7.22	114.65	7.11	40.64	0.00
STAI-Trait	32.45	4.31	32.00	8.37	31.35	9.90	11.40	6.82	34.18	0.00
LSAS	57.63	23.44	31.33	19.17	38.68	22.30	19.05	12.34	24.23	0.00
SASS	32.45	4.31	32.00	8.36	36.68	8.62	39.50	4.45	17.15	0.00
WALDROP	3.00	2.02	4.00	1.86	2.60	2.25	0.16	0.36	29.44	0.00
Hospital del Mar hypermobility of joints criteria	3.50	2.28	1.53	1.06	5.60	1.42	2.30	1.55	35.28	0.00

PANSS: Positive and Negative Syndrome Scale; Medication: Chlorpromazine equivalents from typical and typical antipsychotics; KBIT: Kaufman Brief Intelligence Test; STAI: State-Trait Anxiety Inventory; LSAS: Liebowitz Social Anxiety Scale; SASS: Social Adaptation Self-evaluation Scale; PAS: Bandelow's Panic and Agoraphobia Scale; WALDROP: Waldrop Physical Anomaly Scale. / *H*: Kruskall-Wallis H Test / All groups comparisons were thresholded at *p values* <0.05.

MRI data acquisition and preprocessing

MRI were obtained on a 1.5T Magnetom Vision scanner (GE). Subjects were scanned with a T1-weighted 3D-MPRAGE sequence (TR, 11.6 ms; TE, 4.9 ms; field of view, 230 mm; matrix, 256 × 256; 104 contiguous axial slices of 1.5 mm thickness; voxel size, 1.02 × 1.02 × 2 mm). Every scan was checked for image artifacts and gross anatomical abnormalities. Data preprocessing and statistical analysis were performed using the VBM5 Toolbox (http: //dbm.neuro.uni-jena.de), an extension of the Statistical Parametric Mapping (SPM5) package (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7.0 (The MathWorks, Natick, MA).

We used VBM in order to measure between-group anatomical differences. The VBM identifies differences in the local composition of brain tissue, while determining large scale differences on gross anatomy and position. Fist, we reoriented the images so that the Anterior Comissure is approximately posicionated in the (0, 0, 0) coordanate. Then, we used the VBM5 toolbox to preprocess the images. This toolbox employs and extends the new unified segmentation approach that is implemented in SPM5. The unified segmentation provides a generative model of VBM preprocessing in which tissue classification, image registration, and magnetic resonance imaging are integrated in homogeneous bias correction. The final tissue maps of the GM, white matter (WM), and cerebrospinal fluid (CSF) are modulated with the deformation fields obtained by normalization to standard space in order to analyze volumetrical differences between study populations. For the porpuse of this study, only the GM volume maps were used for statistical analysis. Finally, the modulated GM matter partitions were smoothed with a 12mm FWHM (Full Width Half Maximum) Gaussian Kernel and then entered into the second level analysis.

Results

Clinical Data

The analyses of the clinical data showed significant differences between groups in several of the clinical ratings, as displayed in Table 1. The SQZ/ANX group obtained significant higher punctuation on the LSAS and the Hospital del Mar hypermobility of joints criteria, as compared to the SQZ group. The ANX group scored significantly higher than the control group in the STAI-trait, LSAS and Hospital del Mar criteria. Since the clinical data indicated significant differences in the K-BIT (Kaufman & Kaufman, 1990) we included this test as a nuisance covariate in the performed neuroimaging analyses.

VBM Results

The results of the interaction analysis (Schizophrenia x Anxiety), showed GM volume differences in the right cerebellum, (MNI= x9 -y42 z -43, t=4.00, p<0.001, 553 mm^3), the frontal middle left (MNI= x-38 y33 z45 t=3.75, p=0.001, 133 mm3; MNI= x -34 y16 z59, t=3.47, p<0.001, 32 mm^3), the left middle temporal cortex (MNI= x-53 y-67 z7, t=3.55, p<0.001, 74 mm^3) and the left lyngual gyrus (MNI= x-17 y-68 z4 t=3.15, p=0.001, 12 mm^3). at a threshold of p<0.001 (uncorrected).

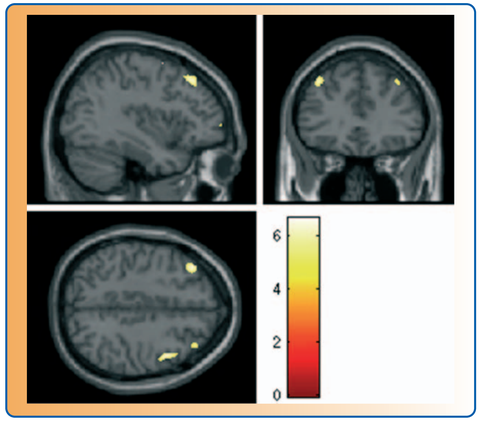
At the selected FWE-corrected threshold of p<0.05, the results of the contrast SQZ/ANX>SQZ> indicated that the SQZ/ANX patients present increased GM volume as compared to patients with SQZ in the precentral right, right middle frontal, left middle frontal, left inferior frontal, left superior frontal, right supramarginal gyrus and right superior frontal (Table 2).

Table 2. Results of the contrast SQZ/ANX>SQZ masked by the interaction contrast (Schizophrenia x Anxiety). Analyses were FWE-corrected at a threshold of *p*<0.05.

Contrast	Brain Region	MNI Coordanates x	y	z	Cluster size (mm^3)	*t*	*p (FWE-corrected)*
SQZ/ANX>SQZ	Right precentral	4 6	4	49	1668	6.69	<0.001
	Right middle frontal	44	17	47		5.11	<0.001
	Left middle frontal	-38	31	45			0.005
		-48	29	30		5.12	0.03
		-34	19	53	831		0.01
	Right middle frontal	37	35	44	148	5.68	0.005
	Left Middle frontal	-41			37	5.35	0.02
	Left superior frontal	-34	59	2	76	5.42	0.01
	Right supramarginal gyrus	65	-19	30	35	5.24	0.02

Furthermore, in order to determine volume differences due to the interaction of Schizophrenia and Anxiety, the interaction contrast (Schizophrenia x Anxiety) (1=SQZ/ANX; -1=SQZ; -1= ANX; 1=Controls) was applied as an inclusive mask to the contrast SQZ/ANX>SQZ (Figure 1). In the contrast SQZ/ANX<SQZ we did not obtained significant results.

Figure 1. Volume differences in the precentral right and bilateral middle frontal cortex as a result of *T* contrast SQZ/ANX>SQZ. The interaction contrast (Schizophrenia x Anxiety) (1=SQZ/ANX; -1=SQZ; -1= ANX; 1=Controls) was applied as an inclusive mask in order to determine GM volume differences corresponding to the interaction of both conditions. Statistical parametric maps were thresholded at *p*<.05 (FWE corrected).



The contrast SQZ<Ctrl was also performed in order to determine GM volume differences among those groups. The results indicated a GMV decrease in the left middle occipital cortex in the SQZ group. The contrast SQZ>Ctrl did not render any significant result at a threshold of p<.05 FWE corrected. Further contrasts between the other groups did not achieved significant results.

Additionally, correlation analyses between the SQZ/ANX group and the extracted regions in the left superior frontal (MNI x-36 y57 z1, t=3.72, p=0.02, 238 mm^3); left middle frontal (MIN x-37 y34 z39; t=1.77, p=0.04, 9 mm^3) and right middle frontal (MNI x39 y32 z41, t=2.32, p=0.01, 47 mm^3) indicated a negative correlation in the Panss Positive Symptoms Subscale. Furthermore, a positive correlation was found in this group between the Hospital del Mar hypermobility of joints criteria scores and the ROIs in the right supra marginal gyrus (MNI x66 y-20 z30, t=2.15, p=0.03, 35 mm^3) and the left inferior frontal (MNI x-47 y28 z27, t=2.15, p=0.02, 17 mm^3).

Conclusions

Our findings suggest that the co-occurrence of schizophrenia and anxiety might be characterized by a specific neuroanatomical and clinical substrate that accounts for schizophrenic and anxiety symptoms and cannot be explained by the presence of either one or both conditions, but by their conjunction, resulting in a determined symptomatology.

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This work was supported by grants from Instituto de Salud Carlos III FEDER, (PI10/00987) and fondo de investigación sanitaria ISCIII,(PI052381)

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