Correlation Between Default Mode Network and Symptomatic Domains: A Spectral Approach to Schizophrenia

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Research Article

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Abstract

Introduction

When evaluating psychiatric pathologies using imaging studies, the categorical approach supposes a significant challenge. Redefining these pathologies with the use of behavioral dimensions that are related to brain biology has been attempted. This paper aims to describe the findings on functional magnetic resonance imaging in patients with schizophrenia and correlate it with their symptomatic domains.

Materials and methods

This study is a descriptive, observational, transversal study. Fourteen patients with schizophrenia and Fourteen controls were explored using functional magnetic resonance during a resting period and developing easy, medium, and complex tasks. The default mode network was evaluated, registering the voxel activation on a cluster and its maximum activation over interest areas. Subjects were interrogated using the Derogatis Symptom Checklist (SCL-90-R) and correlation coefficients were applied for data analysis.

Results

Diminished activation of the default mode network was evidenced in association with the complexity of the task in the control group. Patients presented a steady activation when comparing their resting state with the activation during the different tasks. A negative correlation was observed implicating the volume of the functional cluster in the posterior cingulate cortex during the high complexity task and the interpersonal sensitivity domain. A moderate positive correlation was found with symptomatic domains of interpersonal sensitivity, hostility, phobia, and depression, while a moderate negative association was found with psychosis.

Conclusions

Imaging evaluation of the psychiatric pathologies could be useful if the pathology is approached through the spectrum of symptomatic domains. This perspective would enhance the assertiveness of the therapeutics.

Introduction

Since the origins of psychiatry, mental health has been considered a manifestation of brain pathology. Kraepelin described schizophrenia as early-onset dementia, believing the disease originated from a structural brain anomaly. During the 20th century, efforts were made toward finding anatomopathological evidence on post-mortem mental health patients, with no success [1]. The lack of findings caused a loss

of interest; still, the eagerness to find the etiology of the psychiatric symptoms persisted, especially when treatments like malaria therapy, cardiozolic and electro-convulsive therapies, insulin comas, and the first psychiatric medications showed clinical improvements [2].

In 1976, with the development of Computerized tomography (CT), in vivo visualization of the brain was possible, and lateral ventricle enlargement was documented in patients with schizophrenia (SS). In 1980, Dr. Timothy Crow characterized two types of schizophrenia differenced by clinical aspects, exacerbation with amphetamines, response to antipsychotics, and size of their lateral ventricles on CT [3]. In 1986, Daniel Weinberger studied brain blood flow with inhaled Xenon 133. He discovered that SS did not elevate their frontal lobe flow during complex cognitive tasks, different from healthy subjects (CS) [4], and named it hypo-frontality, calling back the attention to psychiatric functional neuro-imaging to elucidate the origin of psychiatric symptoms.

Functional studies with PET and SPET brought the possibility of measuring glucose metabolism, the brain's blood flow, its distribution, receptor activities, and levels of enzymes and neurotransmitters [5–6]. Nonetheless, the need for radioligands created the urge to reduce radiation without affecting the anatomical, dynamical, functional, and metabolic aspects [7].

Functional Magnetic Resonance Imaging (fMRI) generated the desire to relate functional brain abnormalities with the psychiatric diagnosis. Until now, it has been impossible to determine biomarkers that characterize mental pathologies allowing, through brain imaging, the adequate characterization of the disease, prognosis, the best treatment, and outcomes [5, 7]. The correlation between mental illness and imaging could impact the clinical aspects, aiding in developing an approach strategy that shifts the focus away from the nosological systems (which are categorical and limit the evaluation of the patient). Previous studies have been heterogenic due to differences in psychiatric and psychopathology concepts, as in the methodologies (inclusion criteria, sociodemographic variables, experimental designs, forms of imaging acquisition, processing, and analysis).

The mental disease´s complexity was considered a consequence of the biological and environmental influence, genetics, and epigenetics of multiple systems levels [8]. The evaluation of the behavior (cognition, emotions, social interactions, learning, motivation, and perception) are the visible "tips of the iceberg" when discussing the multiple levels' complexity. However, brain circuits may be the phenotypical expression of the cellular and subcellular, structural and functional, and genetic and epigenetic phenomena. Neural networks, their activation and deactivation processes, and their quantification are crucial elements in understanding the association between the brain and mental illness [9].

The fMRI aids in understanding how mental diseases relate to telencephalic circuits [10]; as such, it is primordial to associate them with the subjacent neuronal network [11]. It has been proposed to redefine them in the dimension of observable behavior, which is aligned with the brain's biology. The NIH considered this and named it the RDoC (Research Domain Criteria) [12–13].

A practical way to mitigate methodological discrepancies in previous studies is by using fMRI [5–7]. The investigation based on symptomatic domains (SD) reflects the characteristics of the circuits and the behavior with an individualized approach, which concord with the singularity of the pathology [8–9, 11]. The DSM-5 proposes to move forward on the dimensional diagnosis stating that using imaging studies, the diagnostic approach should be agnostic about the current nosologic categories of the diseases [13], in favor of creating a correlation between psychopathologic manifestations and structural and functional findings. Following this, the proposed plan is to stop addressing the pathology from the definition and towards the neurobiological bases; but to approach the patient from the clinical aspects and the brain-behavior relationships, considering the relevance of the brain circuits. Multiple analysis elements must be employed, like images, behavior, and symptoms self-reports [2, 14]. The manuscript describes the spectrum of psychopathological symptoms in SS through correlations of the imaging findings on fMRI and the SD obtained with the SCL-90-R.

Methods

Fourteen male SS, according to the DSM-5 criteria, and fourteen CS, paired by gender and age, with no neurological or functional disease were included in the study. The institutional ethical comity approved the study. Every participant signed a consent form.

Clinical evaluation

Full medical records were completed (sociodemographic information, alcoholism, and substance abuse history, personal and familiar pathologic background, and history of cranioencephalic trauma). They were evaluated using the SCL-90-R, the most frequently used tool in Spanish, assessing symptoms over nine different domains: somatization, obsessions, interpersonal sensitivity (SI), depression, anxiety, hostility, phobia, paranoia, and psychosis; and three global psychological discomforts: severity, total of positive signs, and positive symptomatic discomfort.

Image protocol

The fMRIs were acquired in a 1.5 Telsa scanner (Avanto, SIEMENS, Germany). Subjects were indicated to lie supine, with head immobilization inside the antenna. The visual field and sound systems were verified previous to each acquisition. A mirror was placed on the patients' visual field guaranteeing comfortable visualization of a screen where tasks were projected. A T1 sequence from the vertex to the posterior fossa was acquired (FOV = 256 mm, TE = 3.37 ms, TR = 1900 ms, angulation = 15°, slice width = 1 mm, voxel size = 1 mm3). For the functional studies, 20 axial slices were obtained parallel to the tentorium from the vertex to the fourth ventricle using echoplanar sequences (FOV = 240, slice width = 6 mm, TE = 45 ms, TR = 2000 ms, angulation = 90°, voxel size = 3.75 x 3.75 x 6 mm3) with a total of 150 volumes for the task-based fMRI and 200 volumes in resting state.

Acquisition protocol for fMRI

Visual stimuli were performed using videos associated with the tasks and projected inside the scanner room. A first acquisition was performed during a resting phase, and three others were acquired during the low, medium, and high complexity tasks. The executed activities were designed based on nTask operative memory tasks, dividing duties into ten blocks, five for activation and five for control; each performed for 30 seconds (five minutes per task). The low complexity task consisted of remembering the first projected letter from the block and moving the dominant hand's index finger each time the letter was projected again. The medium complexity task consisted of moving the finger when the letter visualized was equal to the one before. The high complexity task consisted of raising a finger when the letter on the screen was identical to the letter projected two slides back. The patient had to focus on a cross projected on the screen for the control block. The different tasks were explained at arrival and reinforced before each sequence.

Data analysis – fMRI processing

Image conversion from DICOM to NIFTI was performed (Compressed FSL – 4D NIfTI nii) using the DCM2NII tool (MRIcro, McCausland Center, Columbia, SC). The data was processed with FSL version 6.0 (FMRIB Software Library, FMRIB Centre, Oxford, UK, www.fmrib.ox.ac.uk/fsl) [15–17]. Movement correction was accomplished using rigid body transform and reducing high-frequency interference without altering the associated neuronal activations. A spacial softening was performed with a gaussian kernel. Temporal high-pass filtering was carried out considering the hemodynamic response signal modeling to eliminate the artifacts associated with the low-frequency noise. Fourier space was used for the synchronization correction of the interleaved slices. Non-cerebral tissues were extracted from the T1 images using the BET tool (Brain Extraction Tool version 2.1, FSL), with a fractional intensity range of 0.5 FIT. This volume was used as a reference in the alignment process and registration using global scale transformations. The standard Montreal Neurologic Institute (MNI152) template was used as a normalization tool using fine transforms. Studies with a displacement higher than 1.5 mm were discarded.

The data processing of the functional sequences was done using the MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components version 3.15, FSL) tool, performing a PICA (Probabilistic Independent Component Analysis). The resulting components were evaluated with FSLeyes to discard those associated with movement and physiologic processes. The specialists identified variables associated with neuronal processes considering the temporal response curve of the frequencies' spectrum and the activation areas. The components' Z statistical maps (Gaussianised T / F) were obtained using clusters determined by $Z > 2.3$, and a p significance = 0.01 was registered with the structural sequences using a lineal BBr transform and the MNI152 brain template using an affine (DOF = 12) transform.

The dorsal and ventral components of the default mode network (DMN) from the Functional Imaging in Neuropsychiatric Disorders (FIND) laboratory at Stanford University were used to evaluate the size of the cluster and the peak of activation in the posterior cingulate cortex (PCC), parietal cortex (PC), and medial prefrontal cortex (MPFC). Values were normalized and registered in maps for each phase. The percentage

of inhibition of the DMN's components was calculated, comparing the volume of the active clusters in the resting state versus the volume of active clusters during each task. The results were represented using the Mango Software (http://ric.uthscsa.edu/mango/).

Statistical analysis

Quantitative variables were expressed in average and standard deviation or median and interquartile ranges. They were analyzed using the non-paired T of student or the U-Mann Whitney, depending on whether they fulfilled the normality assumptions. Relationships between task complexity, SD, and extent and size of the activation cluster of each of the DMN components; were established using correlation coefficients depending on the characteristic of the variable (Spearman, Pearson). A p-value lower than 0.05 was used to indicate statistical significance. Every statistical analysis was conducted using Minitab 18.

Results

Sociodemographic and clinical findings

The average age of the CS was 27.6 ± 7.0, while in the SS was 25.4 ± 8.3, with no statistically significant difference.

SD from the SCL-90-R, had a statistically significant difference in the SS when compared to the CS: somatization ($p = 0.018$), obsessiveness ($p = 0.002$), SI ($p < 0.001$), depression ($p < 0.001$), anxiety ($p = 0.001$), hostility ($p = 0.001$), phobia ($p = 0.019$), paranoia ($p < 0.001$), psychosis ($p = 0.001$) and sickness severity index ($p < 0.001$) (Fig. 1).

Activation extent and cluster size versus. Task complexity

CS presented a statistically significant negative correlation between the complexity of the task and the size of the activation cluster on the PCC ($r = -1.0$) and on the right lateral PC (LPC) ($r = -1.0$), while the correlation was not statistically significant on the MPFC ($r = -0.4$) and the left LPC ($r = -0.4$).

The activation extent presented a statistically significant negative correlation with the complexity of the tasks over the right LPC ($r = -1.0$, $p < 0.01$). On the other hand, a positive correlation was evidenced with the complexity of the task on the MPCF ($r = + 0.6$); there was a negative correlation on the left LPC ($r = -0.4$) and on the PCC ($r = -0.8$) (Figs. 2 and 3). The evidence on the association implicating the variables was not conclusive ($p > 0.05$).

SS had no relationship associating the task's complexity, and the cluster's size activated on the PCC ($r = 0.0$). The significance of the positive correlation with the size of the cluster on the MPCF ($r = + 0.4$), and negative on the left LPC (($r = -0.2$) and right LPC ($r = -0.8$) was not conclusive ($p > 0.05$). On the other hand, the extent of the activation on the MPFC showed a statistically significant positive correlation with the complexity of the task ($r = + 1.0$, $p < 0.01$). Although a positive correlation implicating the complexity

of the task and the extent of the activation of the PCC (r = + 0.4), the left LPC (r = + 0.8) and right LPC (r = + 0.4) were observed (Fig. 4), the significance of the association was not conclusive (p > 0.05).

Activation extent and cluster size versus. Symptomatic domains

The SI dimension showed a statistically significant negative correlation with the activation cluster volume on the PCC during the high complexity task (r = -0.947, p = 0.015) and between the volume of the activation cluster on the same regions during the resting state and the phobia dimension (r = -0.976, p < 0.01). The rest of the domains had no significant correlation with the volume of the activation clusters during the resting phase and the tasks.

DMN inhibition versus. Symptomatic domains

Statistically significant differences were evidenced when relating the percentage of inhibition of the PCC of the CS and the one of the SS (p < 0.01), with no significant differences on other components of the DMN. On the contrary, a moderate positive correlation was evidenced between the amount of inhibition on the PCC and the different domains: SI (r = + 0.6, p < 0.05), hostility (r = + 0.4, p < 0.05), phobia (r = + 0.2, p < 0.05) and depression (r = + 0.2, p < 0.05), and a moderate negative correlation with psychosis (r = -0.2, p < 0.05). A low positive correlation was observed with obsessiveness (r = + 0.1, p < 0.05) and anxiety (r = + 0.1, p < 0.05). A no relationship was evidenced with the somatization and paranoia (r = 0.0, p < 0.05).

Discussion

This manuscript was designed to overcome the difficulties of the psychiatric diagnosis [18] by proposing a dimensional approach using SD and their relationship with neuroimaging markers. The DMN and its activation pattern were studied in the resting state and during three tasks with different complexities. The cerebral function was described and related to the SD evaluated with the SCL-90-R applied on the control subjects (CS) and patients diagnosed with schizophrenia (SS), following the DSM–5 criteria.

The psychiatric evaluation using SD evidenced the difficulties with the diagnosis based on classification systems such as the DSM-5 and the CIE-10 [19]. A group of people may report having common manifestations, categorizing them with a diagnosis of schizophrenia; however, the analysis based on SD allows the clinician to observe the patients' heterogenicity and the broad spectrum of the manifestations. Using a dimensional approach better characterizes the patients, their image findings, and their relation with the best therapeutic choice.

The DMN is a neuronal network constituted by the PCC, the MPCF, PC, and the mesial and inferior temporal lobes. It is associated with reflexive and autoreferential activities. Healthy individuals show a direct relationship between the DMN inhibition and the complexity of the task developed, especially on the PCC and the right LPC. These findings correlate with studies that have demonstrated DMN 's inhibition during cognitive tasks compared to a resting state using nuclear medicine and fMRI [20–25].

Other connectivity studies describe functional and structural relationships implicating the DMN's structures, with minimal disruption during the tasks, revealing the preservation of the network's functionality [26].

DMN has been described in degenerative and psychiatric diseases using fMRI [27]. In SS, there is a functional alteration in the DMN. The activation and inhibition patterns are fundamental in understanding psychopathology [28, 29]. In this study, a lack of inhibition of the DMN was evidenced, predominantly on the PCC, independent of the task's complexity; which could be associated with an absence of a practical assignment of the attention resources on the joyous task networks, which would grant it an essential role in the pathological mechanisms.

It is impossible to create a causal nexus that relates the DMN's disfunction to the cerebral structure anomalies or the neuronal network that maintains the equilibrium. Clinically, the disfunction could alter the shift between introspective and extrospective processes in SS [30]. On the contrary, the lack of relationship between the inhibition and the task's complexity could be secondary to the paradigm of operative memory used in this study [31]. There is evidence associating the abnormal increase in the functional connectivity and the DMN's hyperactivity, even during the early stages, of schizophreniform and schizoaffective disorders, confirming them as part of the physiopathology of the disease [32].

A negative correlation was observed implicating the volume of the functional cluster in the PCC during the high complexity task and the SI domain. As in the previous, the PCC's grade of inhibition was significantly less on the CS than the one on the SS. A moderate positive correlation was found with SI, hostility, phobia, and depression, while a moderate negative association was found with psychosis. In concurrence with preceding studies, the positive symptoms' severity in SS was associated with the neuronal network's functional activity, which may be related to the performance during cognitive tasks and the pathophysiology of the disease [32–33]. This supports the importance of the diagnostic approach using SD.

Evidence suggests the DMN responds to some pharmacological treatments [34–36]. Risperidone has an inhibition pattern closer to the ones shown on CS when compared with the patterns expressed with typical antipsychotics [37], and olanzapine has shown modulation of dopaminergic activity and the DMN response towards different tasks [38]. The previous exhibits the impact of the DMN´s activity on the treatment election and the patients' clinical outcomes. It is a priority to study treatment courses and their relationship to the functional behavior of the DMN.

Even though there was a small sample size, the results of this study were statistically significant. Studies with a higher sample size are required to support the current findings. Given the impact of the treatments on the DMN's function, they should be considered in the inclusion or exclusion criteria to have a homogeneous cohort or to consider them as variables in the statistical analysis of the data. Lastly, longitudinal studies with diagnostic approaches, as the one suggested, may aid in evaluating the activation pattern of the DMN and its variations in relationship with the treatment received and clinical outcomes.

Conclusion

The findings suggest that evaluating psychiatric diseases with fMRI could be of massive utility if a dimensional spectral approach is applied with symptomatic domains. This way, a personalized diagnosis may lead to better patient classifications, and an accurate therapeutic decision, which may influence patient outcomes.

Declarations

Author contributions

Author contributions included conception and study design (AMGS, JFOZ, CAAD and IMA), data collection or acquisition (AMGS, and JFOZ), statistical analysis (JFOZ), interpretation of results (AMGS, JFOZ, CAAD and IMA), drafting the manuscript work or revising it critically for important intellectual content (AMGS, JFOZ, CAAD and IMA) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (AMGS, JFOZ, CAAD and IMA).

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Conflict of interest

The document's authors declare no conflict of interest in the elaboration process or publishing of this article.

Ethics approval

The protocol was revised and approved by the Comité de Ética Institucional of the Fundación Valle del Lili. All the information that could be used to identify them was not included in the manuscript.

Consent to participate

Every patient signed a consent form to participate in the present study.

Consent for publication

No patient photographs were included.

Availability of data and material

All the anonymized data that supports the findings of this study are available from the corresponding author upon request.

Code availability

Not applicable.

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Figures

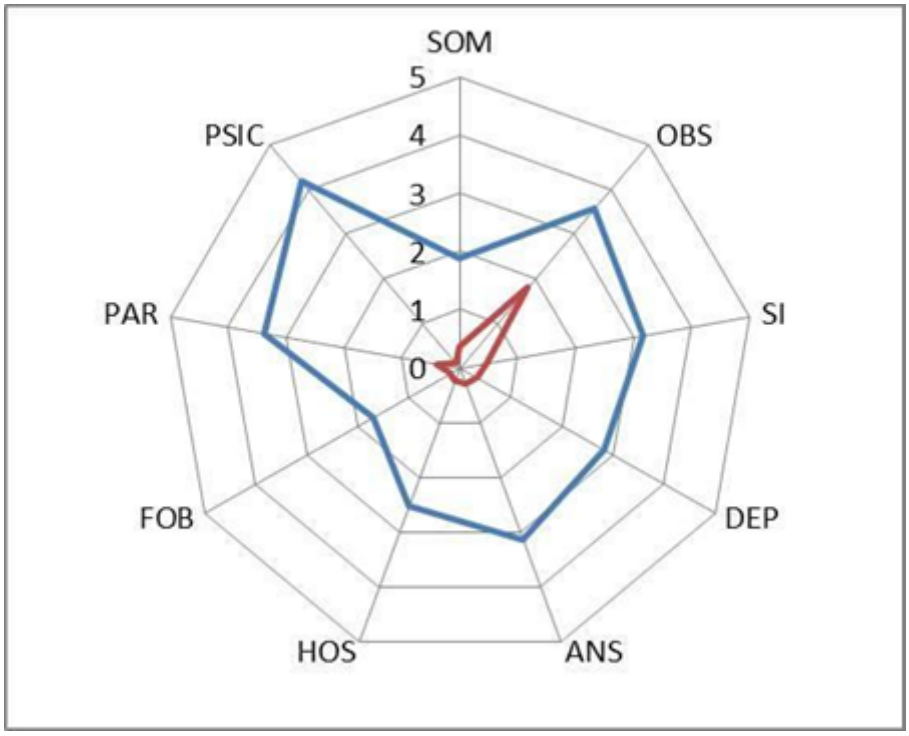

Figure 1

Radial graph showing the results of evaluating the control subjects (red line) and the patients with schizophrenia (blue line), with the symptomatic domains. (SOM: Somatization, OBS: Obsessiveness, SI: Interpersonal sensitivity, DEP: Depression, ANS: Anxiety, HOS: Hostility, FOB: Phobia, PAR: Paranoia, PSIC: Psychosis).

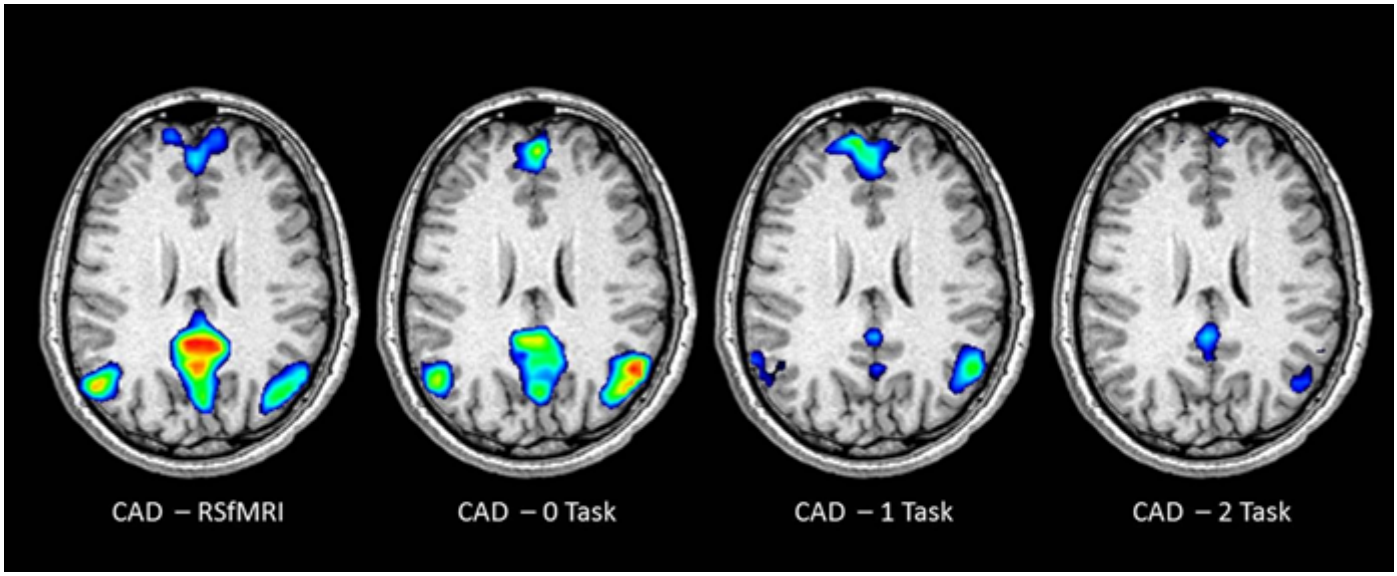

Figure 2

Representative maps showing the activation pattern of the default activation circuit in resting state (CAD - RSfMRI) and during the task of low (CAD - 0 Task), medium (CAD - 1 Task), and high (CAD - 2 Task) complexity in a healthy subject.

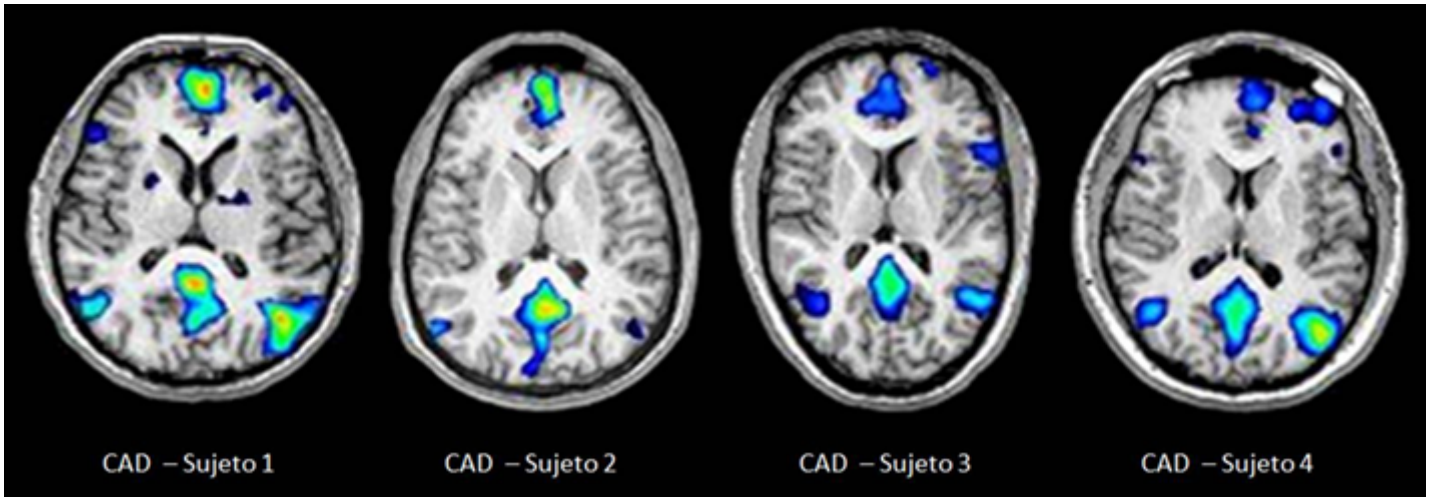

Figure 3

Representative maps of four healthy subjects showing the activation pattern of the default activation circuit during low complexity tasks.

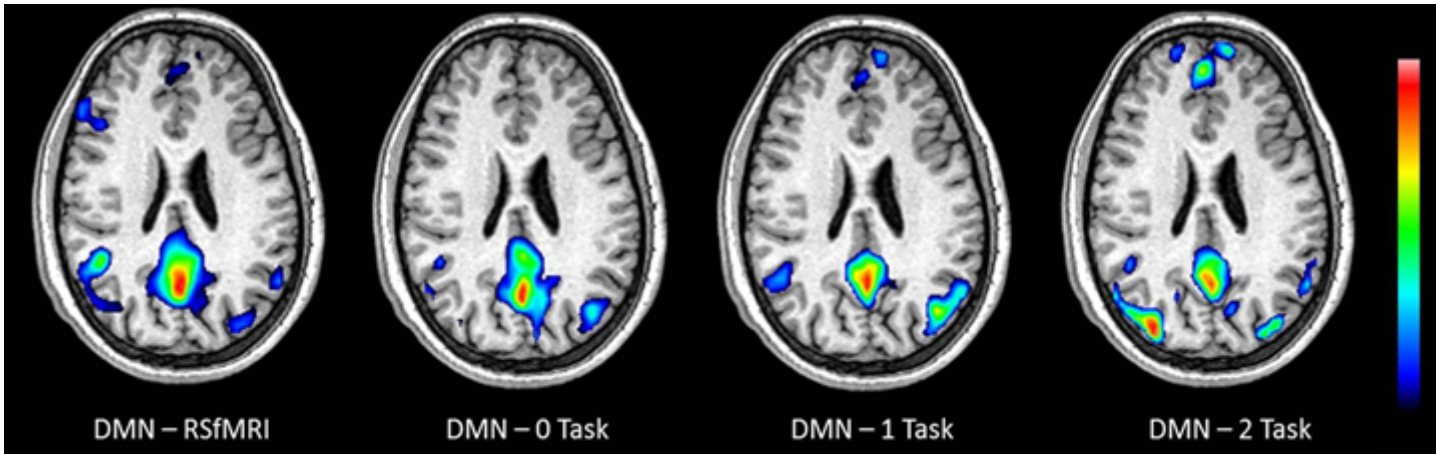

Figure 4

Representative maps showing the activation pattern of the default activation circuit in resting state (DMN - RSfMRI) and during the tasks of low (DMN - 0 Task), medium (DMN - 1 Task), and high (DMN - 2 Task) complexity in a patient with schizophrenia based on the DSM-5 criteria.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AuthorChecklist11682.pdf