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Retrospective Study

Functional Magnetic resonance imaging study of group independent components underpinning item responses to paranoid-depressive scale

Group independent components of paranoid-depressive scale

Abstract

BACKGROUND

Our study expand upon a large body of evidence in the field of neuropsychiatric imaging with cognitive, affective and behavioral tasks, adapted for the fMRI experimental environment.

There is sufficient evidence that common networks underpin activations in task-based fMRI across different mental disorders

AIM

The aim of the current study is investigate whether common and specific neural circuits exist, which underpin differential item responses to depressive, paranoid and neutral items in patients respectively with schizophrenia and major depressive disorder.

METHODS

60 patients were recruited with schizophrenia and major depressive disorder. All patients have been scanned on 3T MRT platform with functional MRI paradigm, comprised of block design, including blocks with items from paranoid (DP), depressive scale (DS) and neutral items (DN) from general interest scale. We performed a two-sample t-test between the two groups – schizophrenia patients (SCZ) and depressive

patients (D). Our purpose was to observe different brain networks which were activated during a specific condition of the task, respectively DS, DP, DN.

RESULTS

Several significant results are demonstrated in the comparison between SCZ and D groups while performing this task. We identified one component that is task-related and independent of condition (shared between all three conditions), composed by regions within the temporal (right superior and middle temporal gyri), frontal (left middle and inferior frontal gyri) and limbic/salience system (right anterior insula). Another component is related to both diagnostic specific conditions (DS and DP) *e.g.* it is shared between D and SCZ, and includes frontal motor/Language and parietal areas. Onespecific component is modulated preferentially by to the DP condition, and is related mainly to prefrontal regions, whereas other two components are significantly modulated with the depression specific condition and include clusters within the default mode network (DMN) such as posterior cingulate and precuneus, several occipital areas, including lingual and fusiform gyrus, as well as parahippocampal gyrus (PHG). Finally, component 12 appeared to be unique for the neutral condition.

In addition, there have been determined circuits across components, which are either common, or distinct in the preferential processing of the sub-scales of the task.

CONCLUSION

This study has delivers further evidence in support of the model of trans-disciplinary cross-validation in psychiatry.

Key Words: Paranoid-depressive scale; functional MRI; cross-validation; group independent component analysis; schizophrenia; depression

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Core Tip: There have been identified five independent components, on the level of brain signals, which are significantly modulated by clinical diagnostic scales adapted to functional MRi paradigm Those results may help potentially to define patterns of activations which differ between patients with depression and patients with schizophrenia

INTRODUCTION

Schizophrenia and depressive disorders constitute 4 % on populational level and are considered severe mental disorders of global health, social and economic burden [1]. Their causal structure and pathogenetic mechanisms remain a controversial topic due to a variety of methodological constraints in psychiatry research [2, 3]. One of those critical constraints is the lack of valid biological markers of disease.

Objective biomarkers have been a critical challenge for the field of psychiatry, where diagnostic, prognostic and theranostics assessments are still based on subjective narratives [4]. The lack of objective biomarkers produces an explanatory gap between disciplines concerned with mental health. On one hand, psychopathology operates with idiographic knowledge and subjective evaluations incorporated into clinical assessment inventories, and on the other hand, it is considered to be a medical discipline and, as such, uses medical intervention methods (e.g., pharmacological, ECT; rTMS; tDCS), and therefore is supposed to operate with the language and methods of nomothetic networks [5].

Yet, there exists a gap between those two kinds of knowledge, which contributes to one major challenge before their integration. As a consequence, the idiographic assessments were provisionally “quantified” into “structured clinical scales” to in some way resemble nomothetic measures. Instead of fostering data merging and integration, this

approach further encapsulates the clinical psychiatric methods, as all other, biological tests (molecular, neuroimaging) are performed separately, only after the clinical assessment has provided diagnosis. By contrast, in other fields of medicine, diagnosis is mandatory co-produced by convergence of biological and clinical evaluation. We expect that neither biological measures nor subjective reports should be considered separately, but contribute to the incremental validity of each other, i.e. regarded as complementary approaches. In this way they can perform better in clinical practice and substitute each other in some clinical situations (like *e.g.* troponin or ECG can substitute radiological tests in some emergency cases).

Translational cross-validation of clinical assessment instruments and fMRI is an attempt to address the gap [4]. It is in line with the emerging attempt to bring together viable imaging data and non-imaging variables, or behavioral components into joint analysis, beyond traditional approaches [6].

Our studies expand upon a large body of evidence in the field of neuropsychiatric imaging with cognitive, affective and behavioral tasks, adapted for the fMRI experimental environment.

There is sufficient evidence that common networks underpin activations in task-based fMRI across different mental disorders [7].

For instance a common behavioral test (which is used as computer adapted test in clinical reality), is monetary incentive task. It has been applied in studies of the reward processing in clinical populations with specific pattern of hypo-and hyper-activation in schizophrenia and depression [8, 9 ,10, 11].

Emotional processing, working memory and reward processing were investigated in various mental disorders with common and distinct signatures of neural circuits' dysfunctions with reactive, regulation and compound fMRI stimuli [12, 13].

A most recent meta-analysis revealed that subjects with depression are reported to have greater activation in the anterior cingulate gyrus, insula, and middle frontal gyrus (MFG) for positive emotional stimuli, whereas activation in the MFG, inferior frontal gyrus, and insula is found to be greater for negative emotional stimuli [14].

In a systematic review by Cusi (2012) social cognition in terms of facial emotion recognition and processing has been reported to be altered in major depressive disorder [15].

Neural correlates of N-back task performance have been consistently reported as correlates of working memory impairments as trans-diagnostic target in different psychiatric disorders, such as schizophrenia, MDD, BD and ADHD [16]. Other working memory tasks have been implemented over the past years to investigate shared and distinct fMRI response in schizophrenia and major depressive disorder [17]. Working memory, cognitive control, prediction error have been studied in schizophrenia, depression and bipolar disorder [18, 19, 12].

Although some of the above mentioned studies implement fMRI tasks with possible clinical use, the results, which address directly the translation between clinical evaluation tools and functional MRI are scarce.

Therefore we decided to explore the fMRI signatures behind the performance on clinical diagnostic self-assessment scales with established reliability and validity [3], whereby diagnostic fMRI tasks are regarded as more "naturalistic" stimuli [20].

Previous results of classical SPM analysis, Depression Scale and Paranoid-Depression Scale

In our previous studies, we have managed to adapt clinical assessment tools to fMRI paradigms (stimuli) and to explore the real-time BOLD signals underpinning item responses [21]. Most prominently we have used two self-assessment tests, which are designed to capture two core syndromes in clinical psychopathology: depressive and paranoid. The two syndromes are captured by the Von Zerssen Depression (DS) and Paranoid-Depressive scales (PD-S). The assumption of our earlier studies was to establish translational validity of the constructs and thereby of the clinical states, without any claims at nosological validity. The depression scale was tested in a population of patients with depression compared to healthy controls. DS stimuli as contrasted to diagnostically neutral scale items yielded in patients with depression

significant residual activations in right supramarginal gyrus, left middle frontal gyrus, triangular part of the left inferior frontal gyrus, and middle temporal gyrus, among others. The left precuneus activation was found to correlate with the patients' DS score [22]. Paranoid-depressive scale was administered in a group of patients with depression compared to patients with schizophrenia. Initial results indicated that patients with schizophrenia demonstrate significant activations in a number of regions (right angular gyrus, left posterior cingulate and precuneus, right transverse temporal gyrus) during responses to paranoid *vs* depressive scale items which differ topologically from those found in patients with major depression (left middle cingulate and right superior temporal gyrus [23]. Further more comprehensive study [24] reported by means of direct comparison significant activations during paranoid items processing in left precuneus and posterior cingulate gyrus and right angular gyrus. Further investigations, using multivariate analysis on a similar sample revealed high discriminatory power of the PD-S as task-related functional MRI paradigm both independently [25] and in combination with other, structural and resting state MRI modalities [26].

As one step further in the implementation of our paradigm, we have decided to use independent component analysis. The method is less focused on voxel-wise analysis, like SPM, and more on identification of temporally coherent spacial networks corresponding to task performance in task-based fMRI [27]. In that context this approach appears to be much more sensitive to capture the fluctuation in the fMRI signal during more complex cognitive-affective tasks, including verbal self-assessment.

Further group ICA was introduced was developed in order to assess independent patterns of network modulation (activation and deactivation) on group level [28].

Group ICA is more agnostic and explorative as compared to general linear model (GLM), essentially multivariate approach, which provides certain degree of freedom in the data interpretation and inferences beyond the constraints of the GLM [29].

In that regard, group independent component analysis (group ICA) on fMRI data with the depression scale adapted to an fMRI task/paradigm [30] confirmed differences in the preferential networks processing diagnostic *vs* off blocks between patients and controls

in anterior cingulate cortex and middle frontal gyrus. In that same study, diagnostic conditions from D-S as contrasted to neutral conditions from interest scale have yielded differential activity of right superior frontal gyrus and right middle cingulate cortex in the comparison of patients with depression and healthy controls.

In this context, the aim of the current study is to investigate whether there exisst common and specific neural circuits, which underpin differential item responses to depressive, paranoid, and neutral items in patients, respectively, with schizophrenia and major depressive disorder. The lead hypothesis is that the item responses to the two scales during fMRI session in patients suffering from the two main spectra of mental disorders may be cross-validated by means of group independent components analysis.

MATERIALS AND METHODS

Subjects

In total, 60 patients participated in this study: 33 with depressive episode (D) and 27 with schizophrenia (SCZ). Initially diagnostic assessment was performed by a board certified psychiatrist using Mini International Neuropsychiatric interview (Sheehan 1998); after that, patients with depression were appraised with Montgomery–Åsberg Depression Rating Scale (MADRS)[1], and patients with schizophrenia with The Positive and Negative Syndrome Scale (PANSS)[2]. We excluded patients with past medical history of concomitant mental conditions, neurological diseases of systemic and organic kind, traumatic incidents with loss of consciousness, or metal implants that interfere with MRI signal. All subjects signed a written informed consent in accordance to the Declaration of Helsinki. Our study was approved by the Medical University of Plovdiv Ethical Committee (ID: P-396/29.05.2015).

Methods

MR Scanning

Patients were scanned on a 3T MRI system (GE Discovery 750w), starting with a high resolution structural scan (Sag 3D T1 FSPGRsequence), slice thickness 1 mm, matrix 256x256, relaxation time(TR) 7.2 ms, echo time (TE) 2.3, and flip angle 12o, followed by

a functional scan (2D EPI sequence), with slice thickness 3 mm, matrix 64 × 64, TR 2,000 ms, TE 30 ms, and flip angle 90°.

fMRI task

The paradigm was comprised of three different active conditions and a resting condition, with a summed duration of 11 min 44 s presented in a standart block design. Each active block went on for 32 s and consisted of four text statements of 8 s each. The statements for the Depression Specific (DS) and the Paranoia Specific (PS) blocks relied on the von Zerssen subscales for depression and paranoia, accordingly, while the Diagnostically Neutral (DN) blocks, was inspired from a questionnaire concerning general likes and interests. Four answers ("completely true", "mostly true", "somewhat true", "not true") with their respective response buttons (upper left, lower left, lower right, upper right) were presented under the questions. Four blocks of each type were rotating between the three active conditions (DS, DN, PS) and the rest condition, when we displayed a cross for fixation. (DS_rest_DN_rest_PS_rest_DS…)

Image Processing

The SPM 12 software [31] was used for the processing thef unctional data. The images were realigned, co-registered with the structural ones, normalized to Montreal Neurological Institute (MNI) space, and smoothed with a 8 mm full-width-at-half-maximum Gaussian kernel.

Independent component analysis (ICA)

To determine the brain networks that were activated in response to the task, a group ICA [32, 33,34] was performed using GIFT software [35]. Individual ICA component maps were calculated using the Infomax algorithm. All subjects were analyzed simultaneously for the group ICA, and principal component analysis (PCA) was used for compression. Because the number of components actually determines the spatial scale of the results (fewer number of the components results in larger brain networks), the number of components in the study was set to 50. The number of components recommended by GIFT based on the data reduction method was about 30, but we

increased it to 50 for extra spatial precision [32,34] . Moreover, such number of components is a typical choice in many studies [36, 37, 38, 39].

A general linear model (GLM) of the activity was constructed for the components by using a single-regression technique with three regressors to evaluate the components which were modulated by the task. The regressors were coded for the three active conditions (DS, DN, and PS). Regression of 50 components resulted from ICA analysis, each indicating the modulation for a particular task. There were single regression analyses for each of 3 conditions and 50 components with the false discovery rate (FDR) correction. The resulting beta values were then used in calculating two-sample t-tests in between-subjects design (SCZ vs. D) to identify significant effects at the FDR corrected $p<0.05$. Thus, we determined the components which were modulated by the task and changed significantly between SCZ and D groups of patients.

We extracted the list of the regions which corresponded to the component activity in MNI and Talairach coordinates by means of "Write Talairach Table" function in GIFT with the following parameters: threshold – 3.5 to ensure $p < 0.01$ while mostly following manual recommendation and the distance between the contiguous voxels – 4 mm, considering smoothing with a 8 mm FWHM Gaussian kernel, as half-width window distance between voxels of smoothed volume could be considered same structure (Radua, *et al* 2014).

Statistical analysis

For the statistical analysis of the demographic and clinical characteristics of the participants we used IBM SPSS 22.0 for Windows. The level of significance was set to $p<0.05$ for all tests. Differences in mean values of continuous variables were tested with Independent Samples Kolmogorov Test and the Pearson Chi-Square test was used for categorical ones.

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[2] Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin*, *13*(2), 261-276.

RESULTS

Results

Demographic and clinical characteristics

The two patient groups did not differ significantly in their sex, education level, and age, also in their age at onset, illness duration and episode duration for the respective condition. as shown in the table. (Table 1).

ICA results

We performed a two-sample t-test for the regressor beta-weights of all independent components between the two groups – schizophrenia patients (SCZ) and depressive patients (D). Our goal was to identify different brain networks, which were activated during a specific condition of the task (respectively, DS, PS, or DN) and differed between SCZ and D groups.

For the DS condition the significant components were – 11, 14, 22, 36 (Table 2, 3 and Figure 1)

For the PS condition, the significant components were – 11, 14, 23, 38 (Table 4, 5 and Figure 2)

For the DN condition, the significant components were – 12, 14, 23 (Tables 6, 7 and Figure 3)

DISCUSSION

This study demonstrated several significant results in the comparison between SCZ and D groups while performing a task with diagnostically specific (for depression and paranoia) and diagnostically neutral stimuli. On the level of independent components,

we identified one component (C14) that is task-related and independent of condition (shared between all three conditions), another component (C11) that is related to both diagnostically specific conditions (DS and PS) and it is shared between D and SCZ, one paranoia-specific component linked only to the PS condition (C38), and two components (C22 and C36) significantly correlated with the depression-specific condition. Finally, component 12 appeared to be unique for the neutral condition.

Component 14 shares significant clusters modulated by all three conditions, therefore it has limited contribution to the differential diagnostic pattern. It is mainly built up by regions within the temporal (right superior and middle temporal gyri), frontal (left middle and inferior frontal gyri) and limbic/salience system (right anterior insula). According to our results, patients with both diagnoses are processing the information by increasing the activity in those regions and on the other hand, independent of the content of the stimuli, the emotional component is always there even in the diagnostically neutral statements. Moreover this could be explained with the semantic processing of emotional words [40, 41], which are likely to have comparable subjective valence for both patients' groups, regardless of the diagnostic-specific content. This component encompasses Brodmann areas (BA) 22, 42, 44, 45 and 47 mainly related to language processing [42, 43], as well as BA 46 which corresponds to the dorsolateral prefrontal cortex (DLPFC) involved in sustained attention and working memory [44, 45]. Moreover, the involvement of the left DLPFC has been linked to higher demands in planning which might be the case of our task with four different response options [46].

Another significant cluster within component 14 appears to be located within the right anterior insula (rAI) which is involved in a variety of cognitive, affective, and regulatory processes, including interoception, emotional reactions, and empathy [47]. Interoceptive processing is suggested to be linked primarily to the function of rAI which is simultaneously part of the salience network (SN) along with anterior cingulate cortex [48] . The crucial role of the SN as a switch between internally (default mode network) and externally (central executive network) oriented attention is found to be disrupted in both SCZ and D [12, 49, 50, 51]. Notably, in our recent effective connectivity

study the alterations of the self-inhibitory connection of the AI emerged as a feature of both mood disorders and SCZ [52].

The second important finding in the present study is that Component 11 is significantly modulated by both diagnostic conditions, DS and PS, thereby contributing to a diagnostic pattern. The brain areas within this component are mainly focused in frontal motor/Language (BA 4,6,8,10,44,45,46) and parietal regions (BA40). Dysregulations in those areas relate to the pathogenesis of both diagnoses – Depression and Schizophrenia [53] and it is expected to be significant in both conditions. Increased activation in Superior frontal gyrus is reported to relate to the different stages of depression [54].

BA10 or rostral prefrontal cortex is involved in working memory, episodic memory, and multiple-task coordination [55] while areas 4, 6, and 8 are related to motor planning. Notably, BA8 demonstrates increased activation with increasing uncertainty in decision-making [56] which might be the case in both patient groups when assessing and responding to diagnostic-specific statements. Interestingly, this component includes supramarginal gyrus (BA40) which is well known for being part of the mirror neuron system, involved in tool use tasks, and visual word recognition as well [57, 58, 59].

Notably, both C14 and C11 include clusters of DLPFC (BA46) where various dysfunctions in task-related fMRI have been found in both SCZ and D [60, 61]. Most studies link the dysfunction to impaired cognitive control which is a manifestation of both pathologies [62, 12] Moreover, on a metabolic level, significant relationship between left DLPFC N-acetilaspartate/creatine ratio and cognitive deficits in patients with first episode psychosis was found [63]. In addition, the role of the left DLPFC in depression is supported by the successful use of this area as a target for transcranial magnetic stimulation in treatment resistant depression [64].

Another finding of our study was the significant difference between SCZ and D in regard to component 38 demonstrating an association with the paranoid-specific items (stimuli). Most of its regions are within the frontal areas of the brain including distributed sensory-motor networks (BA 1,2,3,4,6), and all three sub-divisions of the prefrontal cortex (DLPFC – BA 8,9,46; ventrolateral prefrontal cortex (VLPFC) – BA

45,47; and orbitofrontal (OFC) – BA 10,11). Notably, within this component, the involvement of the well-known language areas BA 44 and 45 extends to a less studied BA47 which is proposed to be part of the "frontal language production system" [65] as well as part of the VLPFC traditionally associated with emotion regulation and cognitive reappraisal. Moreover, the left VLPFC is proposed to be responsible for the semantic process of generating and selecting appraisals according to emotion regulation [66].

The OFC is involved in controlling and correcting reward- or punishment-related behavior, and in emotions [67]. Both structural and functional alterations have been found across a number of psychiatric disorders [68], including SCZ [69] and D [70]. Of note, shared impairment of OFC functional connectivity was found spanning across psychotic and mood disorders with a gradient in the extent of alterations from SCZ through bipolar disorder to major depressive disorder [71]. In addition, resting-state effective connectivity between OFC and precuneus was found to demonstrate differential diagnostic properties in our recent study on SCZ and D [72].

Most of the regions are within the frontal areas of the brain, with DMN and CEN involved as crucial hubs. Studies on the matter have shown significant aberrations in connectivity between the two networks [73], with increased intraconnectivity, while the insula does not display adequate activation, suggesting there may be a circle of a positive feedback mechanism between the two in schizophrenic patients [74]. Furthermore, medial prefrontal cortex is a region, which is associated with high-level executive functions and decision-associated processes [75]. Those functions are impaired in patients with schizophrenia and it is established that they have disrupted function [76, 77]. It is evident that there is significant activation of the postcentral somatosensory cortex, which is consistent with studies documenting increased connectivity between the thalamus and said brain region [78, 79].

Components 22 and 36 are both significantly modulated by the depression specific condition in SCZ as compared to D and thereby contribute to a differential diagnostic pattern. They include clusters within the default mode network (DMN) such as

posterior cingulate and precuneus, several occipital areas, including lingual and fusiform gyrus, as well as parahippocampal gyrus (PHG). PHG has a key role in cognition and memory [80] and is linked to the influence of emotions on these processes [81]. Having in mind the clinical presentation of depression, it is not surprising that this brain region has been implicated in the pathogenesis of the disorder [82]. Research demonstrates that there is an increased involvement of PHG when presenting negative/disgusting stimuli to patients with major depressive disorder [83]. Moreover, whole-brain functional connectivity revealed that the most discriminative connections between patients with depression and healthy individuals were concentrated in the DMN, visual cortex, and affective network and that the PHG has a high discriminative role in terms of the diagnose [84].

Precuneus is known to be a key hub of the DMN, and as such, it plays a crucial role in self-referential processing, including episodic memory and mental imagery. Studies have shown that the precuneus is a potential biomarker associated with MDD [85], further validating the theory of DMN activity alteration in depressive patients, which is also consistent with our findings [86, 73].

The last component which is present in more than one condition is C23, as it appears to be modulated by both PS and DN conditions. The regions within this component are mostly located in the frontal (bilateral DLPFC, OFC, and right VLPFC, pre- and postcentral regions - BA 1,2,3, 6,8,9,10,11,44,45,46) and insular cortex (rAI). The involvement of the SN in this component that is shared between PS and DN conditions might be interpreted as evidence that the diagnostically neutral statements are processed by the patients with schizophrenia as emotionally laden or referential stimuli, as expressed in more detail elsewhere [87].

Component 12 is also significantly higher in SCZ but only in the diagnostically neutral task condition. There are a variety of frontal, temporal, and parietal regions within C12 which are associated with different brain networks – DMN (precuneus, angular gyrus,

medial PFC), CEN, language (semantic) network. Given the nature of the task, it is expected to see regions connected with language processing, working memory and attention. However, the Medial frontal gyrus, as region of conducting complicated processes, decision making [75] also yields in the component. What is more, it is negatively correlated. This finding proposes the idea that even if the stimuli is on the neutral side, for the patients it has meaningful interpretation and is beyond their rational control.

Apart from its contribution to the DMN, angular gyrus (AG) has been described as a "core facility used by different subsystems to access concepts when interfacing perception-to-recognition-to-action" [88]. According to the authors, the AG should be seen as cross-modal integrative hub attributing meaning to an event within a context, based on prior expectations, and aimed at an intended action. As part of the semantic network, AG is engaged in reading and comprehension, and in schizophrenic patients' severity of formal thought disturbances was correlated with a disruption of the left semantic network [89]. Interestingly, subjects with SCZ demonstrate and abnormal asymmetry of the AG (left smaller than right) as compared to healthy controls (left larger than right) which might have contributed to the present results [90].

It is noteworthy that there are common, shared and distinct regions from all components, which seem to form disrupted brain networks, which process the task conditions in different ways between the two nosological groups. The main disrupted networks are – DMN, CEN and SN, with an executive summary presented on Table 8.

This adds evidence to the model of translational validation, established in our earlier work with case-control design [72]. Complementary to the already reported distinct (or specific) circuit, processing depressive scale in depressed patients, we have discovered a specific network processing paranoid items in the current specificity study. The latter includes left superior frontal gyrus and its continuation – the left medial frontal gyrus. Superior frontal gyrus is liked to self-awareness [91]. The disturbances of self-awareness are core phenomenological manifestations of psychosis [92]. Our findings are consistent

with the findings of other authors about dysregulations of functional connectivity in the same region associated with schizophrenia [93] as well as with our own previous studies [24].

The shared circuits which process DP and DS including components from the fronto-parietal network [93] are likely to reflect the convergence of psychosis and affective disorders on the level of the underlying neural mechanisms,

We assume that the activated insula in both conditions (DS and DP) reflects the impaired role of switching the functions between default mode network (DMN) and central attention networks (CEN) [74]. In contrary to many studies which yield decreased function of the insula in our study we find an increased function of the regions. We hypothesize that the increased function of the insula may compensate the disruptions in the other two networks – DMN and CEN, as a higher level of control. That assumption is in line with other studies, which report abnormal regulations of the task-positive and task-negative networks [94] as well as reduced suppression of DMN during semantic processing in schizophrenia.

Limitations

This study has several limitations. The first is the relatively small sample size. However the current practice of fMRI studies states that the sample size we use is sufficient for the analysis we are conducting. Szucs and Ioannidis [95] conclude that highly cited clinical fMRI studies (with patient participants) had median sample size of 14.5 subjects. Moreover, Desmond and Glover [96] state that for a liberal threshold of 0.05, about 12 subjects were required to achieve 80% power at the single voxel level for typical activations. At more realistic thresholds, that approach those used after correcting for multiple comparisons, the number of subjects doubled (24 subjects) to maintain this level of power. Also, under ongoing grant funding, our group plans to expand the sample and to outsource independent replication studies. The second limitation is methodological, as GIFT is considered to be liberal approach to brain imaging data analysis when compared to SPM more stringent techniques. The third limitation is the absence of a healthy control group. It is entailed from the assumption that in this

design, we explore rather specificity, i.e., differences across disorders. This is not in dissonance with the overall research rationale and is complemented with a study of sensitivity under another research project [23, 24]. Although current treatment is sometimes considered as a potential confound, the effects of medication in depression have been reported in most recent voxel-based meta-analysis as having limited impact. In other terms alterations are likely to persist regardless to the medications status of the patients [97].

CONCLUSION

This study has delivered evidence in support of the model of trans-disciplinary validation in psychiatry. The model has been previously tested using the same PD-S with classical SPM analysis and with multivariate linear method, which provide other perspectives on the same methodological concern [98]. In summary, that methodological question is whether and to what extent is it possible to cross-validate neuroimaging state-dependent biomarkers with clinical state-dependent assessment scales. Although we are still far away from the ultimate answer to such question, nevertheless this is a piece of progress towards better attunement between brief clinical tests used in everyday practice and fMRI as a potential external validator. Further replications are called for in order to advance in this line of investigation.

In broader perspective those results navigate the way to bridge the explanatory gap between psychopathology and neuroscience. Psychopathology is operating with common sense narratives, structured into clinical scales, when neuroscience operates with biological measures. The traditional assumption is that narratives, i.e. clinical scales need to refer to the gold standard of neuroscience, when both groups of methods are actually very controversial. With this work we propose a paradigm shift towards better translation of the clinical assessment tools into neuroimaging findings and vica versa.

ARTICLE HIGHLIGHTS

Research background

The background of this study is comprised of earlier contributions of our group. Those contributions include studies of the functional MRI correlates of the item responses to paranoid and depressive self-assessment scales. Those were studies on patients with depression, schizophrenia, and healthy controls, by means of statistical parametric mapping and multivariate linear method.

Research motivation

The research motivation for the current study is to investigate the modulation of the functional MRI signals by the diagnostic specific task (paranoid-depressive scale) with more complex toolbox. The group independent component analysis for FMRI toolbox (GIFT).

Research objectives

The primary objective of the study were to reveal the modulation of fMRI signals by diagnostic specific scales item responses in two clinical populations: patients with schizophrenia and depression. The secondary objective was to investigate the difference in those signatures across the groups.

Research methods

The methods include clinical assessment, functional MRI, statistical methods and GIFT.

Research results

The results indicate that there exist different neural circuits, which are modulated by paranoid and depressive diagnostic specific tasks. There are reported differences in the modulation of those circuits between patients with schizophrenia and depression.

Research conclusions

The methodology of GIFT is appropriate for translation of functional MRI findings into clinical utility.

Research perspectives

There are perspectives in the application the same methodology to other clinical assessment scales, *e.g.* for state and trait anxiety as well as for independent replications of the current findings.

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