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Interindividual variability of brain activity in schizophrenia

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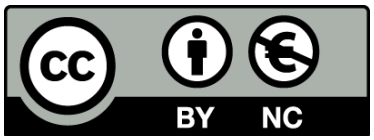

Interindividual variability of brain activity in schizophrenia

Memòria de tesi doctoral presentada per **Aniol Santo Anglès**

per optar al grau de doctor per la Universitat de Barcelona,

dirigida per:

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Research Foundation

Programa de Doctorat Medicina i Recerca Translacional

Facultat de Medicina i Ciències de la Salut. Universitat de Barcelona

Desembre 2021

Barcelona, a 30 de novembre de 2021

A l'atenció de la Comissió Acadèmica del programa de doctorat de Medicina i Recerca Translacional, Facultat de Medicina de la Universitat de Barcelona

Amb el present escrit, Dr. Miquel Bernardo Arroyo i Dr. Edith Pomarol-Clotet, com a co-directors de tesi del doctorand Aniol Santo Angles, donem el vist i plau a la presentació de la seva tesi doctoral, titulada 'Interindividual variability of brain activity in schizophrenia'.

Per a que així consti, firmen el present

Miquel Bernardo Arroyo

Edith Pomarol-Clotet

Aniol Santo Angles

Als meus pares, Pere i Pilar,

a Caterina i a la nouvinguda.

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TESI EN FORMAT DE COMPENDI D'ARTICLES

La tesi consta de 3 objectius, 2 articles publicats i un manuscrit amb resultats no publicats.

1. Primer objectiu: validació en població sana de la tasca de ressonància magnètica funcional CMET, Computerised Multiple Elements Test, d'avaluació ecològica de funcions executives.
    a. Fuentes-Claramonte P, **Santo-Angles A**, Argila-Plaza I, Lechón M, Guardiola-Ripoll M, Almodóvar-Payá C, et al. Brain imaging of executive function with the computerised multiple elements test. Brain Imaging Behav. 2021;15(5):2317–29. doi: 10.1007/s11682-020-00425-0.
    b. Factor d'impacte, quartil i àrea de coneixement:
        i. Segons Scimago Journal & Country Rank, consulta del 9 de novembre de 2021, la revista Brain Imaging and Behavior te un H-index de 1.239, situada en el primer quartil de l'area de Neurociencia, i al primer quartil de l'area de Medicina, categoria Psiquiatria i salut mental.
        ii. Segons Journal Citation Reports, consulta del 9 de novembre de 2021, la revista Brain Imaging and Behavior te un impact factor (2020) de 3.978, un 5 year impact factor de 4.046, i esta en el segon quartil de la categoria Neuroimaging.

2. Segon objectiu: estudi dels correlats cerebrals de la disfunció executiva en esquizofrènia per mitja de la tasca CMET i ressonància magnètica funcional.
    a. Resultats no publicats inclosos a la tesi doctoral sota el titol "Apathy-avolition symptoms and executive dysfunction in schizophrenia: fMRI study with ecological assessment of goal management".

3. Tercer objectiu: estudi de la variabilitat interindividual en el connectoma funcional en esquizofrènia.
    a. **Santo-Angles A**, Salvador R, Gomar JJ, Guerrero-Pedraza A, Ramiro N, Tristany J, et al. Interindividual variability of functional connectome in schizophrenia. Schizophr Res. 2021;235(January):65–73. doi: 10.1016/j.schres.2021.07.010.
    b. Factor d'impacte, quartil i àrea de coneixement:
        i. Segons Scimago Journal & Country Rank, consulta del 9 de novembre de 2021, la revista Schizophrenia Research te un H-index de 1.923, situada en el primer quartil de l'area de Neurociencia, i al primer quartil de l'area de Medicina, categoria Psiquiatria i salut mental.
        ii. Segons Journal Citation Reports, consulta del 9 de novembre de 2021, la revista Schizophrenia Research te un impact factor (2020) de 4.939, un 5 year impact factor de 5.058, i esta en el primer quartil de la categoria Psiquiatria.

RESUM DE LA TESI

Variabilitat interindividual de l'activitat cerebral en l'esquizofrènia

INTRODUCCIÓ

L'esquizofrènia és un trastorn psiquiàtric complex amb una important variabilitat interindividual en els símptomes clínics, el deteriorament cognitiu, el pronòstic i la resposta al tractament, probablement perquè representa una síndrome heterogènia en lloc d'una malaltia discreta. L'estudi de la variabilitat interindividual de la funció cerebral pot ajudar a abordar aquesta heterogeneïtat i guiar la recerca de subgrups de pacients amb substrats fisiopatològics comuns, facilitant el desenvolupament de noves dianes farmacològiques i estratègies terapèutiques personalitzades. Aquesta tesi doctoral presenta un conjunt de treballs originals que avaluen la variabilitat interindividual de l'activitat cerebral evocada per tasques i en estat de repòs mitjançant ressonància magnètica funcional.

Els símptomes negatius en l'esquizofrènia segueixen sent un repte terapèutic no satisfet. Es pensa que els símptomes negatius, especialment els dèficits motivacionals i l'apatia-avolició, s'associen a la disfunció executiva, donada la similitud amb els símptomes dels pacients neurològics amb lesions prefrontals. No obstant, els estudis de neuroimatge han proporcionat una evidencia limitada a aquesta hipòtesi, probablement perquè les tasques cognitives utilitzades per avaluar les funcions executives solen obviar la naturalesa multitasca de les situacions de la vida real, sent incapaces de capturar les dificultats que els pacients amb esquizofrènia pateixen en el món real.

En aquesta tesi doctoral, es presenta la validació, en població sana, d'una tasca de ressonància magnètica funcional que avalua les funcions executives de manera ecològica, amb l'objectiu de capturar l'activitat cerebral associada a la disfunció executiva en situacions de la vida real. A continuació, s'estudien les anomalies cerebrals associades a la disfunció executiva i els símptomes negatius en pacients crònics amb esquizofrènia, així com les alteracions en

variabilitat interindividual. Finalment, en una mostra independent de pacients, s'aborda la variabilitat interindividual del connectoma funcional i s'estudien les propietats topològiques de les xarxes en estat de repòs mitjançant una anàlisi de teoria de grafs.

HIPÒTESIS

1. Durant l'execució de la tasca de ressonància magnètica funcional dissenyada per avaluar la gestió de metes de manera ecològica, els subjectes sans activen xarxes cerebrals associades al control cognitiu i funcions executives, i la seva activació es correlaciona amb el rendiment conductual.

2. Els símptomes negatius en l'esquizofrènia, especialment els dèficits motivacionals i l'apatia, s'associen a una disfunció executiva a nivell conductual i neuronal, però la detecció d'aquesta associació requereix una avaluació ecològica de les funcions executives.

3. L'esquizofrènia s'associa a anomalies funcionals en la variabilitat interindividual de l'activitat cerebral en repòs i durant l'execució de tasques cognitives. L'anàlisi de la variabilitat podria permetre la discriminació entre patrons comuns i divergents d'anomalies, i la identificació de possibles subgrups biològics de pacients.

OBJECTIUS

1. Validació en ressonància magnètica funcional, en una mostra de controls sans, d'una tasca de funcions executives dissenyada per avaluar de manera ecològica la gestió de metes i el monitoratge del rendiment, la Computerized Multiple Elements Test (CMET).

2. Avaluació dels correlats neuronals de la disfunció executiva en l'esquizofrènia per mitjà de ressonància magnètica funcional i la tasca CMET. Les anàlisis principals inclouran la comparació dels patrons d'activació entre pacients i controls, la correlació de l'activitat cerebral associada a la tasca amb la severitat dels símptomes negatius, i l'avaluació de la variabilitat interindividual en l'activació cerebral durant la tasca.

3. Estudi de la variabilitat interindividual del connectoma funcional en l'esquizofrènia, mitjançant dades de ressonància magnètica funcional en estat de repòs, i l'associació amb les propietats topològiques de les xarxes cerebrals funcionals i la severitat dels símptomes clínics.

MÈTODES

Les funcions executives es van avaluar mitjançant la tasca Computerized Multiple Elements Test (CMET), una adaptació per a ressonància magnètica del Modified Six Elements Test (MSET), dissenyada per avaluar d'una manera ecològica la gestió de metes i el monitoratge del rendiment, imitant les demandes cognitives polièdriques de les situacions de la vida real. Mentre els subjectes realitzaven la tasca, vam adquirir dades de ressonància magnètica funcional. L'activitat cerebral associada a les funcions executives es va avaluar mitjançant un model lineal general (General Linear Model, GLM) a nivell individual i grupal. Les anàlisis estadístiques es van realitzar a cada vòxel de forma independent (voxel-wise massive-univariate approach), incloent la comparació de l'activació cerebral entre els grups de pacients i controls, i la correlació amb la severitat dels símptomes negatius, controlant pels efectes de confusió d'edat, sexe, coeficient intel·lectual premòrbid i actual, i el moviment del cap durant l'adquisició de dades de ressonància. Per caracteritzar la variabilitat interindividual de les respostes evocades per la tasca, vam calcular mapes de superposició (overlap) i mapes de desviació. Els mapes de superposició descriuen la consistència entre subjectes dels patrons d'activació cerebral, mentre que els mapes de desviació quantifiquen el grau individual de desviació en l'activació cerebral respecte al seu propi grup, permetent una anàlisi estadística de la variabilitat.

La variabilitat interindividual de l'activitat cerebral en estat de repòs es va realitzar de la següent manera. El connectoma funcional, a nivell individual i grupal, es van calcular mitjançant correlacions parcials de les series temporals de dades de ressonància magnètica funcional obtingudes de diferents regions cerebrals. A continuació, vam quantificar la variabilitat interindividual dins del grup comparant connectomes funcionals individual i grupal mitjançant tres mètriques de distància: distància euclidiana i geodèsica, i dissimilaritat de Pearson. Finalment, vam comparar aquestes mesures de variabilitat entre pacients i controls, i les vam correlacionar amb la severitat dels símptomes clínics i les mesures d'integració i segregació funcional derivades de l'anàlisi de grafs.

RESULTATS PRINCIPALS

La tasca Computerized Multiple Elements Test (CMET) va ser capaç de capturar activacions cerebrals, dependents del rendiment durant la tasca, a les xarxes bàsiques que suporten el control cognitiu i les funcions executives, les xarxes frontoparietals ('central executive') i cingulo-operculars ('salience'). Els pacients amb esquizofrènia van mostrar alteracions en el rendiment de la tasca, que suggereixen dèficits en la gestió de metes, associades amb hipoactivació a l'ínsula anterior dreta, el còrtex cingular anterior dorsal, i gir angular bilateral. L'anàlisi de la variabilitat va revelar que les regions hipoactives en pacients també presentaven anomalies en la variabilitat interindividual. Addicionalment, regions prefrontals medials es van mostrar associades amb patrons divergents d'hipo/hiperactivació en funció de la severitat dels símptomes negatius.

La variabilitat interindividual en el connectoma funcional es va mostrar incrementada en pacients amb esquizofrènia, en comparació amb els controls sans, però la variabilitat no es va distribuir de manera igual a tot el còrtex. Les xarxes d'estat en repòs ('default mode network') i frontoparietal ('central executive') van mostrar una major variabilitat en pacients, mentre que la xarxa cingulo-opercular ('salience network') va mostrar una major homogeneïtat en els pacients. A més, les anàlisis de correlació entre la variabilitat del connectoma funcional i els símptomes clínics, tanmateix com la correlació entre la variabilitat del connectoma funcional i les mètriques derivades de la anàlisis de grafs, van mostrar que el connectoma funcional mitjà dels pacients sobreestimava les deficiències d'integració funcional i la severitat dels símptomes clínics.

CONCLUSIÓ

L'anàlisi de la variabilitat interindividual s'ha revelat com a un enfocament que proporciona informació útil sobre patrons comuns o divergents d'anomalies cerebrals en els pacients. Els resultats de la tasca CMET i de la anàlisis de connectivitat funcional en estat de repòs han revelat una anomalia comuna entre pacients a nivell de xarxa cingulo-opercular ('salience network'), d'acord amb la hipòtesi de la disfunció de la triple xarxa, que atribueix un paper central a la xarxa cingulo-opercular (en particular, a l'ínsula anterior dreta) en les anomalies globals de connectivitat cerebral que presenten els pacients amb esquizofrènia. A més, l'anàlisi de variabilitat en la tasca CMET ha revelat que regions prefrontals medials estaven associades a patrons divergents d'hipo/hiperactivació en funció de la severitat dels símptomes negatius, especialment amb dèficits motivacionals, proporcionant evidencia en favor de la hipòtesi executiva (frontal) dels símptomes negatius.

THESIS SUMMARY

Interindividual variability of brain activity in schizophrenia

INTRODUCTION

Schizophrenia is a complex psychiatric disorder with an outstanding interindividual variability in clinical symptoms, cognitive impairment, prognosis and treatment response, probably because it represents a heterogeneous syndrome instead of a discrete disease entity. The study of interindividual variability of brain function might address such heterogeneity and guide the search for subgroups of patients with common pathophysiological substrates, facilitating the development of new pharmacological targets and personalized therapeutic strategies. The current doctoral thesis presents a set of original works that assessed interindividual variability of task-evoked and resting-state brain activity using functional Magnetic Resonance Imaging.

Negative symptoms in schizophrenia remain as an unmet therapeutic challenge. It is thought that negative symptoms, particularly motivational deficits and apathy-avolition, are associated with executive dysfunction, given the similarity of symptoms with neurological patients suffering from prefrontal lesions. However, brain imaging evidence supporting this hypothesis have been limited, probably because the cognitive tasks used to assess executive functions usually neglect the multitasking nature of real-life situations, failing to capture real-world difficulties of patients with schizophrenia.

Here, we validated an fMRI task in healthy population that assess executive functions in an ecological way, aiming to capture brain activity associated with executive dysfunction in real-life situations. Then, we studied brain abnormalities associated with executive dysfunction and negative symptoms in chronic patients with schizophrenia, as well as patients' alterations in interindividual variability. Finally, in an independent sample of patients, we

addressed intersubject variability of functional connectome and studied the topological properties of resting-state networks through a graph theory analysis.

HYPOTHESES

1. During the execution of the fMRI task designed to assess goal management in an ecological way, healthy subjects activate brain networks associated with cognitive control and executive functions, and its activation correlates with behavioral performance.

2. Negative symptoms in schizophrenia, particularly motivational deficits and apathy, are associated with executive dysfunction at behavioral and neural level, but the detection of such association requires an ecological assessment of executive functions.

3. Schizophrenia disorder is associated with functional abnormalities in intersubject variability of brain activity at rest and during the execution of cognitive tasks. Variability analysis might allow the discrimination between common and divergent patterns of abnormalities, and the identification of potential biological subgroups of patients.

GOALS

1. Functional MRI validation, in a sample of healthy controls, of a task of executive functions designed to assess goal management and task monitoring in an ecological way, the Computerized Multiple Elements Test (CMET).

2. Assessment of the neural correlates of executive dysfunction in schizophrenia with fMRI and CMET task, comprising case-control comparison of mean activation patterns, correlation with negative symptoms severity, and the evaluation of intersubject variability in brain activation during the task.

3. Study of interindividual variability of functional connectome in schizophrenia, by means of resting-state fMRI data, and its association with the topological properties of resting-state networks and clinical symptoms severity.

METHODS

Executive functions were assessed using the Computerised Multiple Elements Test (CMET), a scanner friendly adaptation of the Modified Six Elements Test (MSET), designed to assess goal management and task monitoring in an ecological way, mimicking the multifaceted cognitive demands of real-life situations. While subjects performed the task, we acquired functional MRI data. Brain activity associated with executive functions was assessed using General Linear Model at individual and group level. Statistical analyses were performed using a voxel-wise massive univariate approach, including the case-control group comparison of brain activation, and its correlation with negative symptoms severity, controlling for the confounding effects of age, sex, premorbid IQ, current IQ and head motion. In order to characterize intersubject variability of task-evoked responses during the executive functions task, we computed overlap and deviation maps. Overlap maps described between-subjects consistency of brain activation patterns, while deviation maps quantified the individual degree of deviation in brain activation with respect to its own group, allowing a statistical analysis of variability.

Interindividual variability of resting-state brain activity was performed as follows. Individual- and group-level functional connectomes were computed using partial correlation of fMRI timecourses of atlas-based brain parcellations. Then, we quantified within-group interindividual variability by comparing individual and within-group functional connectomes through three distance metrics: euclidean and geodesic distance, and Pearson's dissimilarity. Finally, we compared these measures of functional connectome variability between patients with schizophrenia and healthy controls, and correlated them with clinical symptoms severity and graph-derived metrics of functional integration and segregation.

MAIN RESULTS

The Computerized Multiple Elements Test (CMET) was able to capture performance-dependent brain activations in the core networks supporting cognitive control and executive functions, frontoparietal (central executive) and cingulo-opercular (salience) networks. Patients with schizophrenia showed CMET task performance impairments, suggestive of goal management deficits, associated with hypoactivation in right anterior insula, dorsal anterior cingulate and bilateral angular gyri. Variability analysis revealed that patients' hypoactivated regions also presented abnormalities in intersubject variability, and additional medial prefrontal regions appeared to be associated with divergent patterns of hypo/hyperactivation depending on negative symptoms severity.

Interindividual variability of functional connectome was higher in patients with schizophrenia, in comparison with healthy controls, but variability was not equally distributed throughout the cortex. Frontoparietal and default mode networks showed greater variability, while salience network appeared to be more homogeneous across patients. Furthermore, correlation analyses between variability of functional connectome and both clinical symptoms and graph-derived metrics showed that patients' group-average functional connectome overrepresented functional integration impairments and clinical symptoms severity.

CONCLUSION

Interindividual variability analysis revealed to be a useful approach, providing information about common or divergent patterns of brain abnormality across patients. Results from CMET task and resting-state fMRI data converged into a common abnormality at the level of salience network, in agreement with the triple network dysfunction hypothesis that attributes a central role to the salience network (right anterior insula in particular) in the large-scale connectivity abnormalities in schizophrenia. Furthermore, variability analysis on CMET task revealed that medial prefrontal regions were associated with divergent patterns of hypo/hyperactivation depending on negative symptoms severity, particularly with motivational deficits, supporting the dysexecutive (frontal) hypothesis of negative symptoms.

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder suffered by approximately 1% of the world's population (1,2), generally leading to severe functional impairment in several domains of daily life (3), and reducing the life expectancy by 20 years compared with general population (3). It is thought to originate from brain development disruptions caused by genetic and/or environmental factors (4,5), with a major, but not exclusive, involvement of the dopaminergic system in the origins and development of psychotic symptoms (6).

Brain imaging studies, summarized in recent meta-analyses, have provided strong evidence of structural brain abnormalities associated with schizophrenia disorder (7–11). Van Erp and colleagues (7) reported widespread reduction of cortical thickness and cortical surface area in patients with schizophrenia, in comparison with healthy controls, predominantly in frontal and temporal cortical regions. Vita and colleagues (11) reported progressive changes in cortical gray matter predominantly affecting the left (dominant) hemisphere and superior temporal regions, particularly in the first stages of the disease. Subcortical regions are also affected in patients with schizophrenia, in terms of widespread reductions in gray matter volume (8), structural shape and asymmetry (9).

Some of these abnormalities might be associated with antipsychotic medication (7,12,13), although brain structural abnormalities are already present in drug-free patients with first-episode psychosis (FEP) (13,14) and even before the psychosis outbreak, at prodromal phases (10). Radua and colleagues (13) reported gray matter volume reductions in medial frontal / anterior cingulate cortices and bilateral insula in naïve-medication FEP patients, while Gao and colleagues (14) extended these findings reporting gray matter volume reductions in drug-free FEP patients in frontotemporal regions, bilateral medial posterior cingulate/paracingulate gyrus, bilateral insula, basal ganglia and left cerebellum. In a meta-analysis of structural MRI studies, Jalbrzikowski and colleagues (10) found that individuals at clinical high risk who later on developed psychosis showed reduced cortical thickness in bilateral paracentral, right fusiform, and left superior temporal regions, when compared with individuals at risk with no psychotic outbreak and healthy controls. No abnormalities were found in surface area or subcortical volumes.

Functional magnetic imaging resonance (fMRI) studies have also provided robust evidence of functional brain abnormalities in patients with schizophrenia. Meta-analyses on resting-state fMRI studies reported abnormalities in

functional connectivity (15,16), consistent with the dysconnectivity hypothesis of schizophrenia (17,18). Dong and colleagues (16) reported within- and between-network dysconnectivity in central executive, salience and default mode networks, in comparison with healthy controls, suggesting that imbalanced communication between salience and both default and frontoparietal networks may underlie the core difficulty of patients to differentiate self-representation and environmental salience processing. Moreover, Brandl and colleagues (15) found that patients with schizophrenia, in comparison with patients with other psychiatric disorders (e.g., bipolar disorder, major depression, addiction and anxiety), showed hypoconnectivity in the same brain networks (i.e., central executive, salience and default mode networks), in addition to the limbic network. Connectivity abnormalities and gray matter volume reductions converged in insula, lateral postcentral, striatum and thalamus.

Task-evoked brain activity also revealed functional abnormalities in patients with schizophrenia. Minzenberg and colleagues (19) meta-analyzed fMRI studies of executive functions, including delayed match-to-sample, N-back, AX-CPT, and Stroop tasks. Patients with schizophrenia and healthy controls activated overlapping distributed brain networks, including frontoparietal (central executive), cingulo-opercular (salience) and subcortical nuclei. Group comparison showed reduced activation in patients, in comparison with healthy controls, in bilateral dorsolateral prefrontal cortex (PFC), right ventrolateral PFC, rostral/dorsal anterior cingulate cortex (ACC), premotor regions, posterior areas in temporal and parietal cortices, and left thalamus. On the contrary, patients hyperactivated ventrolateral PFC, several midline premotor cortical areas, temporal and parietal regions, insula and the amygdala, interpreted as compensatory responses.

Patients with first-episode psychosis also showed abnormalities in brain activations during cognitive tasks in brain regions with gray matter volume reductions (13,14). Radua and colleagues (13) reported reduced activation in patients in medial frontal, anterior cingulate cortex and bilateral insula, while Gao and colleagues (14) reported hypoactivations in right angular, inferior frontal and insula, but hyperactivations in left superior temporal, right striatum and left fusiform gyrus. Unaffected relatives of patients with schizophrenia also showed functional brain abnormalities (20–22). In a meta-analysis of tasks involving executive functions, Goghari and colleagues (22) reported hypo- and hyper-activations in right middle frontal regions depending on task requirements. In a meta-

analysis of cognitive and emotional tasks, Scognamiglio and colleagues (20) reported widespread hyper-activations in frontal, temporal and parietal regions, and focal hypoactivations in cingulate cortex, in unaffected relatives of patients in comparison with healthy controls. In a meta-analysis of working memory tasks, Zhang and colleagues (21) reported hypoactivations in right middle and inferior frontal areas, and hyperactivations in right frontopolar, left inferior parietal and bilateral thalamus, in unaffected relatives compared with controls.

In summary, MRI studies strongly suggest that structural and functional abnormalities in schizophrenia concentrate in multimodal associative areas comprising high-level cognitive brain networks, such us frontoparietal (central executive), cingulo-opercular (salience) and default mode networks. Moreover, brain abnormalities are also present, but attenuated, in medication-naïve patients with first-episode psychosis and healthy subjects genetically at-risk (i.e., unaffected relatives of patients).

Neuroimaging biomarkers

Despite the strong evidence of structural and functional brain abnormalities described above, no neuroimaging biomarkers are available to assist diagnostic, prognosis and treatment in schizophrenia (23,24). Several methodological factors may explain this situation, such as the proliferation of studies with small sample sizes with statistically significant findings but negligible clinical or biological relevance (25), the lack of replications but the abundance of 'approximate replications' that neither confirms nor refutes (26), and the comparison between prototypical (or extreme) cases of psychiatric patients and healthy controls healthier than the general population (27). Small sample sizes can be partially addressed through meta-analysis, although the heterogeneity of methods limits the conclusions that can be drawn from them (28). Other authors pointed out the need to move forward from significance testing into out-of-sample predictions validity, which requires samples of several hundreds of observations (29).

Nevertheless, the lack of biomarkers in schizophrenia in particular, and psychiatry in general, goes beyond the field of brain imaging (26). Several lines of research pointed out the lack of biology grounded definitions of mental

diseases (30–32), suggesting that schizophrenia represents an heterogeneous syndrome instead of a discrete disease entity (33,34). This might explain the counterintuitive fact that increasing the sample size does not always reduce sample heterogeneity, as expected, but rather increases it (35).

For all these reasons, the focus of interest in the field of biological psychiatry has gradually moved beyond the traditional framework of case-control studies, which implicitly assumed common etiopathology and neurobiology for all patients with a psychiatric diagnostic of schizophrenia disorder. Early attempts to address heterogeneity focused on the identification of homogeneous clinic subtypes of patients, such as the deficit syndrome (36), or the study of neurobiological correlates of dimensions of psychopathology within schizophrenia disorder (37) and, more recently, across disorders (38,39).

A step forward into the dimensional approach in psychiatry came with the Research Domain Criteria (RDoC), a research framework designed to focus the research on biological psychiatry on empirically based domains instead of diagnostic groups (40–44). RDoC describes a set of domains (negative valence, positive valence or cognitive systems, among others) defined by some constructs (anxiety or fear for negative valence; several aspects of reward processing for positive valence; and cognitive control, working memory, attention or perception for the domain of cognitive control systems). This framework relies on the assumption that dimensions of psychopathology correspond to abnormalities in some of these mechanistic constructs, but this hypothesis must be empirically tested (43).

Another way to identify biological subtypes of patients with schizophrenia and/or biomarkers of psychopathology dimensions comes from the study of interindividual variability (45–47), under the assumption that increased intersubject variability in brain structure or function might indicate heterogeneous underlying pathophysiological mechanisms while decreased variability suggests a common abnormality (48,49).

The following sections summarize the main findings of the dimensional approach in schizophrenia, particularly regarding negative symptoms, cognitive control and executive dysfunction. Later on, we will address the study of interindividual variability in brain structure and function in schizophrenia.

Dimensions of psychopathology

Patients exhibit a myriad of psychotic symptoms, including delusions, hallucinations and disorganized behavior (positive symptoms), motivational deficits, apathy or avolition, social withdrawal, expressivity deficits and incapacity to feel pleasure or anhedonia (negative symptoms), and cognitive deficits, including dysfunctions in working memory, attention, verbal fluency, processing speed and executive functioning (4). However, the clinical manifestation of the disorder shows an outstanding inter- and intra-subject variability (37,50,51).

From a categorical perspective, the traditional clinical subtypes of schizophrenia in Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Statistical Classification of Diseases and Related Health Problems (ICD) tried to address such heterogeneity, but the lack of clinical validity and research utility led to its removal in the last editions of the DSM-V and ICD-11 (52–54). Other proposals focused on negative symptoms, such as 'deficit syndrome' (36), or 'persistent negative symptoms' (55). Deficit syndrome defines a subgroup of patients with persistent and primary negative symptoms, i.e., symptoms not derived from secondary factors such as positive or cognitive symptoms, depression, anxiety or social isolation (36). Persistent negative symptoms defines a subgroup of patients with enduring negative symptoms regardless of their etiology, particularly designed for the context of clinical trials (55). Kirkpatrick and colleagues (56) proposed that patients with deficit syndrome constitute a separate disease within the schizophrenia syndrome since deficit and non-deficit patients differ in their signs and symptoms, course, biological correlates, treatment response, and etiologic factors. Since then, evidence supporting the validity of deficit syndrome accumulated (57–60), but most findings have not yet been replicated (59) and it remains unclear whether deficit syndrome reflects a separate disease entity or just the extreme end of a severity continuum (61). Brain imaging studies exemplifies this situation. The evidence suggests that patients with deficit syndrome, in comparison with non-deficit patients, show gray matter abnormalities, e.g., gray matter volume (GMV) and/or cortical thickness reductions. However, studies highly differ in the location of these abnormalities. Lei and colleagues (62) reported GMV reductions in cerebellar culmen in first-episode patients. In chronic patients with deficit syndrome, Cascella and colleagues (63) reported GMV reductions in bilateral superior frontal and temporal gyri, left supplementary motor area, left anterior cingulate, left cuneus and right putamen; Fischer and colleagues (64) found

GMV reductions in superior prefrontal and superior and middle temporal gyri; Takayanagi and colleagues (65) found cortical thinning in anterior cingulate cortex, and Xie and colleagues (66) reported a more widespread cortical thinning in deficit patients, particularly in the left temporo-parietal junction area. Small sample sizes might explain the divergent results between studies (59), although a recent meta-analysis showed no volumetric differences between deficit and non-deficit patients (67). Inconsistent findings have also been reported about persistent negative symptoms (68).

From a dimensional perspective, negative symptoms have recently been reconceptualized from the traditional unitary into a multidimensional construct (69). Early studies with factor analysis on clinical symptoms scales (e.g., Positive and Negative Syndrome Scale, PANSS; Scale for the Assessment of Negative Symptoms, SANS; and Schedule for the Deficit Syndrome, SDS) suggested the existence of two domains of negative symptoms: motivational deficits, including avolition, anhedonia and asociality, and diminished expressivity, including blunted affect and poverty of speech (70,71). It led to the development of new rating scales of negative symptoms accounting for that distinction (72,73): the Clinical Assessment Interview for Negative Symptoms (CAINS) (74) and the Brief Negative Symptom Scale (BNSS) (75). Further research consistently showed that these domains were associated with different profiles (76). Avolition-apathy patients, in comparison with expressivity deficit group, showed more severe disorganization symptoms, poorer premorbid and current social functioning, greater social cognition deficits, and higher likelihood to have a gradual psychotic onset and to be male. Moreover, evidence from clinical trials suggested that avolition constitutes a core symptom within the constellation of negative symptoms, and a successful treatment of avolition might result in a global improvement (77), making it a potential target for pharmacological development (78).

Most research on the neural substrates of avolition-apathy domain have focused on reward processing (72). Patients with schizophrenia present preserved hedonic responses but abnormalities in reward prediction, reward learning and reward-dependent action selection, although their association with motivational deficits have not always been clear (79,80). In a meta-analysis of ventral striatum (VS) responses during reward processing, Radua and colleagues (81) found that negative symptoms severity was associated with left VS hypoactivation during reward anticipation and reward feedback, although a posterior meta-analysis did not replicate this finding (82). However, none of these

meta-analyses discriminate between negative symptoms domains. Mucci and colleagues (83) reported that deficit patients showed hypoactivation of dorsal caudate nucleus during reward anticipation, in comparison with non-deficit patients and healthy controls. Interestingly, patients with high scores in avolition showed the same pattern of hypoactivation, relative to patients with low avolition, but anhedonia showed no association with reward processing abnormalities. Morris and colleagues (84) confirmed the association between avolition/apathy symptoms and dorsal caudate dysfunction during the integration of action-outcome learning. Motivational deficits have also been associated with deficits in the representation of value (85,86), but other studies did not confirmed it (87,88). Abnormal effort-cost computations has also been linked to negative symptoms (89–91), but also see (92–94). Despite some inconsistencies, evidence suggest that different aspects of reward processing, particularly reward prediction and reward-based action, are associated with motivational deficits, but not with the expressivity deficits (72,80).

Expressivity deficits domain of negative symptoms has been associated with neurocognitive or social cognition deficits (72,95). Blunted affect might arise from abnormalities in emotion identification and discrimination, and the perception of nonverbal social information (96,97), or, alternatively, from motor expressivity deficits (98–100). Alogia have been associated with verbal fluency (101) and it is thought to emerge from cognitive resource deficits (102).

Nevertheless, recent evidence suggests that the latent structure of negative symptoms might goes beyond the aforementioned two dimensions. Two well-powered factor analyses (103,104), and a meta-analysis (105), confirmed the multi-dimensional structure of negative symptoms, concluding that the complexity of negative symptoms is better captured by a hierarchical model with a latent structure of five consensus domains, i.e., avolition, anhedonia, asociality, blunted affect and alogia, or by a hierarchical model nesting the five domains into the dimensions of avolition-apathy and expressivity deficits.

The mixture of evidence supporting both dimensional and categorial approaches on negative symptoms led some authors to propose hybrid categorical-dimensional models, where categories allow for within-group severity

(106,107), which might explain divergent findings concerning persistent negative symptoms (68) and deficit syndrome (59).

Executive functions in schizophrenia

Executive functions, also referred as executive control or cognitive control, are defined as a set of top-down mental processes including inhibition, working memory and cognitive flexibility, from which are built reasoning, problem solving and planning (108). They comprise a set of mental abilities responsible for organization and planification, anticipation and attention, initiation of activity, self-monitoring, control impulse, working memory, mental flexibility, feedback usage and selection of strategies for problem-solving (109). Cognitive control can also be defined as the set of processes involved in the generation and maintenance of proper task goals, suppression of no longer relevant goals, as well as the engagement of attentional biases according to goal representations that allows the improvement of task performance (110). In the current work, we considered cognitive control and executive functions as interchangeable concepts. However, it is worth to mention that cognitive control and executive functions might define slightly different constructs. Cognitive control refers to the set of mechanisms engaged during the execution of a task that demands flexibility, while executive functions define a broader construct implicating long-term goal representations and the hierarchical structure of goals and subgoals at different time scales (111,112).

Data-driven approaches to identify cognitive constructs underlying executive functions highlighted its multidimensional nature. Factor analysis over five frequently used executive tasks showed that executive functions can be understood as three separable functions: mental set shifting, information and monitoring, and inhibition of prepotent responses (113). However, posterior factor analysis over 19 executive functions tests reported six factors comprising prospective working memory, set-shifting and interference management, task analysis, response inhibition, strategy generation and regulation, and self-monitoring and set-maintenance (114).

Research Domain Criteria (RDoC) defines the domain of cognitive control as "A system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context. Additionally, control processes are engaged in the case of novel contexts, where appropriate responses need to be selected from among competing alternatives"; and comprises the subconstructs of a) Goal Selection, Updating, Representation, and Maintenance, b) Response Selection; Inhibition/Suppression and c) Performance Monitoring (115).

Cognitive deficits are a core symptom of schizophrenia (116–118), with 80% of patients showing clinically significant cognitive impairments (119,120). Cognitive deficits are present in first-episode drug-free patients (121), get stablished before the prodromal stages of the disease (122), and remain relatively stable after psychosis onset (116,123), supporting the neurodevelopmental nature of schizophrenia (117,124). Cognitive deficits are better predictors of functional outcome than positive psychotic symptoms (125–127). Interestingly, in a 5-year longitudinal study of deficit syndrome and functional outcome, Galderisi and colleagues (128) found that avolition and expressivity deficits were associated with different dimensions of functional outcome: social outcome for the former, while functioning in household activities in the latter. In a 1-year longitudinal study, Fervaha and colleagues (129) found that cognitive impairment and amotivation at baseline were both independently associated with functional outcome at follow-up, suggesting that both domains are separable (130).

Cognitive dysfunction spans all cognitive domains, such as processing speed (131,132), working memory (133), attention/vigilance (134), verbal learning (135), visual learning (136), social cognition (137,138), and executive functions or cognitive control of behavior (139). However, it is a matter of debate whether cognitive impairment in schizophrenia is general (132,140–143) or domain-specific (144–146).

Among the myriad of cognitive dysfunctions present in schizophrenia, executive dysfunction might constitute a nuclear deficit (147). Dysexecutive symptoms are present in chronic patients with schizophrenia (139,148), medication-free first-episode patients (149), and also unaffected first-degree relatives of patients and adolescents at risk of development of psychosis (148,150,151). However, deficits in other cognitive domains are also present at

different stages of the disease (152,153). In a meta-analysis of executive dysfunction in schizophrenia, Thai and colleagues (139) reported a global executive impairment in all subtests if the BADS scale (Behavioral Assessment of the Dysexecutive Syndrome) in chronic patients with schizophrenia, in comparison with healthy subjects. Interestingly, executive dysfunction was not equally distributed throughout the BADS subtests. The effect size of case-control differences was larger for the most complicated subtests, involving complex executive subdomains, than for the simplest tasks. Indeed, cognitive control of behavior in general, and the most complex executive subdomains in particular, requires the coordinated engagement of other impaired cognitive domains, such as working memory or attention.

Negative symptoms and executive dysfunction

It is though that negative symptoms in schizophrenia, particularly motivational deficits and apathy-avolition, are associated with executive dysfunction, given the similarity of symptoms with patients suffering from lesions in dorsomedial prefrontal or anterior cingulate cortices (150,154–157). Indeed, negative symptoms and executive dysfunction are correlated, although the effect sizes are weak-to-moderate (158–160). In a meta-analysis of cognitive impairment in deficit syndrome, Bora and colleagues (60) reported more severe cognitive impairment in deficit patients, in comparison with non-deficit, in all cognitive domains and all individual tasks. In a study with a large sample, Fervaha and colleagues (161) also reported a generalized cognitive impairment in patients with deficit syndrome, in comparison with non-deficit patients. However, when the authors compared deficit patients with non-deficit patients with negative symptoms (i.e., non-primary and/or non-persistent negative symptoms), significant group differences disappeared, suggesting that cognitive impairment is associated with negative symptoms independently of duration and etiology. Moreover, a discriminant analysis on cognitive scores between deficit and non-deficit misclassified one-third of individuals, leading the authors to conclude that deficit subtype is not markedly different from non-deficit subtype. Patients with persistent negative symptoms have also been associated with executive dysfunction in first-episode patients (162), but negative results have also been reported (163,164).

Nevertheless, none of the preceding studies addressed the association of executive dysfunction with different domains of negative symptoms. In contrast, Roth and colleagues (165) found more severe executive dysfunction in chronic patients with high levels of apathy, in comparison with patients with low apathy, and Faerden and colleagues (166) reported an association between apathy and executive dysfunction in a large sample of first-episode psychosis patients. However, Hartmann-Riemer and colleagues (91) found an association between executive dysfunction and diminished expressivity, but not apathy, in chronic patients with schizophrenia. However, the absence of association between apathy-avolition and executive dysfunction might be driven by the small sample size and the restricted assessment of executive functions, limited to working memory and mental planning.

Brain imaging studies with large sample sizes have provided support to the frontal hypothesis of negative symptoms. A multi-site MRI study reported a negative correlation between negative symptoms severity and left middle orbitofrontal cortex thickness (167), but the multidimensional nature of negative symptoms was not considered in the study. In a study of latent clinical-anatomical dimensions, Kirschner and colleagues (168) reported orbitofrontal-striatal structural abnormalities associated with negative symptoms at different stages of schizophrenia spectrum. Cortical thinning in orbitofrontal cortex was associated with negative symptoms in patients with first-episode psychosis, and the degree of cortical thinning appeared associated with illness duration and medication dose. However, healthy individuals with schizotypy presented thicker orbitofrontal cortex compared with all groups. Moreover, apathy was negatively association with putamen/accumbens volumes in healthy individuals with schizotypy, but not in patients with first-episode or chronic schizophrenia. Importantly, these results were discovered in one dataset and replicated in three independent samples.

However, to our knowledge, there is no consistent neural evidence supporting the link between prefrontal abnormalities associated with executive dysfunction and motivational deficits or apathy-avolition in schizophrenia (72,169). The lack of ecological validity in the assessment of executive functions may have contributed to it (170). Most studies used neuropsychological tests and cognitive tasks (19,108,171) with poor ecological validity that fail to generalize to daily-life situations (172,173). For example, such instruments usually assess executive functioning throughout the evaluation of its components separately (e.g., planification and anticipation, initiation of activity,

self-monitoring, working memory, mental flexibility and problem solving), neglecting the multitasking and open-ended nature of real-life situations, failing to capture real-world difficulties of patients with schizophrenia (174–176). It led to a growing interest in the development of more ecological instruments for the assessment of executive functions (170,177,178), including the Computerized Multi Elements Test (CMET) (179,180), an scanner friendly adaptation of the Modified Six Elements Test (MSET), a neuropsychological test designed to assess self-regulation of behavior and goal management (178), able to capture deficits in task monitoring and goal neglect in first-episode (149,181) and chronic patients with schizophrenia (182,183).

Variability on brain activity

Biological heterogeneity of schizophrenia has long been recognized (184), but it has recently received much attention (47,185), since it might help to identify biological subtypes of patients with schizophrenia and/or biomarkers of psychopathology dimensions (49,186), in line with the goal of 'precision psychiatry' (187). In a meta-analysis of variance of striatal dopamine function, Brugger and colleagues (48) reported that dopamine synthesis and release capacities showed no increased interindividual variability in patients, suggesting that they may represent core features of the disorder. On the contrary, availabilities of dopamine receptors D2/3R and dopamine transporter DAT as well as synaptic dopamine levels showed higher intersubject variability in patients, suggesting the existence of subgroups of patients that may contribute to variability in treatment response and side-effects.

Brain imaging studies also reported structural abnormalities in variability in schizophrenia. In a meta-analysis of regional brain structural abnormalities in schizophrenia, Brugger and colleagues (49) reported greater variability in volumes of putamen, temporal lobe and thalamus in patients, but lower variability in the volume of anterior cingulate cortex, in comparison with healthy controls. According to the authors, heterogeneity in biological processes underlying the disorder might explain differences in variability, i.e., greater heterogeneity in patients might indicate distinct biological subtypes, while reduced variability may suggest the presence of common abnormalities shared across the disorder. In another study with a large sample size, Alnæs and colleagues (188) found higher heterogeneity in patients with schizophrenia in cortical thickness, cortical surface area, and cortical

volumes widespread throughout the cortex, in addition to ventricular and hippocampal volumes. However, no regions with lower variability were reported. Interestingly, polygenic risk score was associated with cortical thinning in frontotemporal regions, but not with heterogeneity, suggesting that interindividual variability might emerge from the interaction gen-environment that might not be captured by genetic risk factors.

Abnormalities in variability of resting-state networks and functional connectivity in schizophrenia have also been reported. Gopal and colleagues (189) found greater spatial heterogeneity in resting-state networks in schizophrenia, particularly in basal ganglia, bilateral temporal, sensorimotor and visual networks. Chen and colleagues (190) also reported higher variability in the spatial distribution of brain networks in primary sensory areas, and greater variability in the functional connectome in patients with schizophrenia, in comparison with healthy controls. More recently, Sun and colleagues (191) reported higher intersubject variability in functional connectome in bilateral sensorimotor, visual, auditory and subcortical regions. Interestingly, the authors also reported that functional connectivity heterogeneity was positively correlated with clinical heterogeneity, but negatively correlated with clinical symptoms severity.

Task fMRI studies that address interindividual variability of task-evoked brain activity in schizophrenia are scarce. Dickinson and colleagues (192) used PANSS negative and distress composite scores to cluster patients using an unsupervised data-driven subgrouping analysis, and identified subtypes of patients with different profiles in demographic, diagnostic, clinical, cognitive and personality variables. Deficit subgroup showed more severe negative symptoms and was more likely associated with cognitive and educational impairment, and symptoms of disorganization. Distress subgroup showed more severe distress and positive symptoms, with elevated dysphoric personality traits, and were more likely to be prescribed with mood medications, sedatives and multiple medications. Low-symptom subgroup showed the lowest levels of symptoms and cognitive dysfunction, and higher levels of global functioning. Interestingly, Dickinson and colleagues conducted an exploratory analysis with fMRI data with n-back task, and reported distinct patterns of neural recruitment during working memory. The low-symptoms subgroup showed greater activation in right dorsolateral PFC, in comparison with the other subgroups. Deficit subgroup showed greater activations in parietal cortex, probably compensatory responses, while distress subgroup

showed widespread pattern of hypoactivation suggestive of a global failure to both canonical circuits of working memory and compensatory responses. Despite the limitations of this study (e.g., chronic patients, no replication in an independent sample), it clearly suggests that data-driven identification of clinical subtypes of patients might help to address heterogeneity, as well as to understand the pattern of hyper- and hypo-activations reported in task fMRI studies in schizophrenia.

In the current doctoral thesis, I present three original works that address the topics described in the introduction. First, the published article entitled 'Brain imaging of executive function with the computerised multiple elements test' (193) presents the CMET task, a scanner friendly task particularly designed to capture cognitive control and executive functions in a more ecological way than the conventional cognitive tasks of executive functions. Here, we presented the fMRI validation of the task in healthy population and its adaptation to be used in clinical populations with executive dysfunction. Second, the article entitled 'Apathy-avolition symptoms and executive dysfunction in schizophrenia: fMRI study with ecological assessment of goal management' contains unpublished fMRI data with the CMET task in a relatively large sample of chronic patients with schizophrenia. This study addressed the assessment of group differences in mean activation as well as interindividual variability in brain activity associated with executive functions. Third, the published article entitled 'Interindividual variability of functional connectome in schizophrenia' (194) characterized intersubject variability in resting-state networks in a large sample of chronic patients with schizophrenia and healthy controls, assessed its association with clinical symptoms severity, and performed a graph theoretical analysis of brain networks.

HYPOTHESES

1. During the execution of the fMRI task designed to assess goal management in an ecological way, healthy subjects activate brain networks associated with cognitive control and executive functions, and its activation correlates with behavioral performance.

2. Negative symptoms in schizophrenia, particularly motivational deficits and apathy, are associated with executive dysfunction at behavioral and neural level. To identify such association, we introduced the following novelties:

    a. An ecological assessment of executive functions that allows the acquisition of fMRI data while patients were engaged in a task of goal management and task monitoring.

    b. An assessment of negative symptoms based on the distinction between the dimensions of a) apathy-avolition, and b) expressivity deficits.

3. Schizophrenia disorder is associated with functional abnormalities in intersubject variability of brain function both at rest and during the execution of a cognitive task. The study of interindividual variability allow us to:

    a. Discriminate between common and divergent patterns of brain abnormalities in patients with schizophrenia.

    b. Detect subgroups of patients with different profiles of brain activity.

GOALS

1. Functional MRI validation, in a sample of healthy controls, of a task of executive functions designed to assess goal management and task monitoring in an ecological way, the so-called Computerized Multiple Elements Test (CMET).

2. Assessment of the neural correlates of executive dysfunction in schizophrenia with fMRI and CMET task, including:

    a. Group comparison of brain activation patterns between patients with schizophrenia and healthy controls, matched by age, sex and premorbid IQ.
    b. Correlation analysis between brain activation during the task and negative symptoms severity, considering the distinction between domains of apathy-avolition and expressivity deficits.
    c. Evaluation of intersubject variability in brain activation during the task.

3. Study of interindividual variability in resting-state functional connectivity in patients with schizophrenia and healthy controls, comprising:

    a. Assessment of different distance metrics to assess intersubject variability in matrices of functional connectivity.
    b. Description of the topological properties of brain networks by means of a graph theory analysis of functional integration and segregation.
    c. Evaluation of the association between intersubject variability in the functional connectome, and the topological properties of brain networks or the severity of clinical symptoms.

METHODS AND RESULTS

Brain imaging of executive function with the computerized multiple elements test

Goal 1. Functional MRI validation, in a sample of healthy controls, of a task of executive functions designed to assess goal management and task monitoring in an ecological way, the Computerized Multiple Elements Test (CMET).

Fuentes-Claramonte P, **Santo-Angles A**, Argila-Plaza I, Lechón M, Guardiola-Ripoll M, Almodóvar-Payá C, et al. Brain imaging of executive function with the computerised multiple elements test. Brain Imaging Behav. 2021;15(5):2317–29. doi: 10.1007/s11682-020-00425-0.

Brain Imaging and Behavior (2021) 15:2317–2329
https://doi.org/10.1007/s11682-020-00425-0

ORIGINAL RESEARCH

Brain imaging of executive function with the computerised multiple elements test

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Accepted: 1 December 2020 / Published online: 26 January 2021

Abstract

The Computerised Multiple Elements Test (CMET) is a novel executive task to assess goal management and maintenance suitable for use within the fMRI environment. Unlike classical executive paradigms, it resembles neuropsychological multi-elements tests that capture goal management in a more ecological way, by requiring the participant to switch between four simple games within a specified time period. The present study aims to evaluate an fMRI version of the CMET and examine its brain correlates. Thirty-one healthy participants performed the task during fMRI scanning. During each block, they were required to play four simple games, with the transition between games being made either voluntarily (executive condition) or automatically (control condition). The executive condition was associated with increased activity in fronto-parietal and cingulo-opercular regions, with anterior insula activity linked to better task performance. In an additional analysis, the activated regions showed to form functional networks during resting-state and to overlap the executive fronto-parietal and cingulo-opercular networks identified in resting-state with independently defined seeds. These results show the ability of the CMET to elicit activity in well-known executive networks, becoming a potential tool for the study of executive impairment in neurological and neuropsychiatric populations in a more ecological way than classical paradigms.

Keywords Executive function · fMRI · Resting-state · Goal · Brain networks

Paola Fuentes-Claramonte and Aniol Santo-Angles share the first authorship.

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Introduction

Goal management and its alterations are often assessed with multi-elements tasks like the Modified Six Elements Test (MSET, Wilson et al. 1996) or the Hotel Test (Manly et al. 2002), where the subject is required to execute different sub-tasks necessary to achieve an overall goal. These tasks require planning, strategy, working memory, prospective memory and response monitoring, and are able to predict everyday executive performance problems in brain-injured individuals (Renison et al. 2012). Brain imaging studies have shown that goal management and maintenance relies upon two brain functional networks that are generally involved in executive function: the fronto-parietal network (FPN), which comprises the dorsolateral prefrontal cortex (DLPFC) as well as lateral and inferior parietal areas (intra-parietal sulcus, inferior parietal cortex), and the cingulo-opercular network (CON), spanning the dorsal anterior cingulate cortex (dACC) and the anterior insula/frontal operculum region (Cai et al. 2016;

Dosenbach et al. 2006, 2007; Lopez-Garcia et al. 2016). These networks emerge not only in executive tasks, but also during resting-state as intrinsic functional networks characterized by synchronous activity (Allen et al. 2011; Power et al. 2011; Raichle 2011; Yeo et al. 2011).

Brain imaging of goal management and maintenance, however, has not traditionally used multi-elements tasks but classical attention, inhibition or switching paradigms, which have proven very useful to study executive function but which are also limited in that they show little resemblance to real-world situations (Burgess et al. 2006) and sometimes might not capture executive deficits in patients with brain injury or psychiatric disorders that, despite normal performance in these tasks, show impairments in everyday activities (Burgess et al. 2009). There is a need for generalizable, ecologically valid experimental paradigms to study executive function and executive impairments in brain imaging.

An aspect that has prevented the use of goal management tasks that, like the MSET, resemble real-life situations is that they are difficult to adapt to the fMRI environment due to the timing and movement constraints required by this technique, but efforts have been made. The Computerised Multiple Elements Test (CMET), described in Hynes et al. (2015) and Cullen et al. (2016) was developed to serve as a scanner-friendly test of goal management and goal neglect. In the original task, the participant was asked to play four games in two conditions: in the executive condition (voluntary switching), instructions required playing each game twice per block, dedicating the same time to each game, while in the control condition (prompted switching) participants had to switch games when prompted by the experimenter. Their pilot study showed good convergent validity of the task with the MSET and the Hotel Test in a sample of participants with brain injury. They also showed, in 12 healthy subjects, that performing the task and specifically performing voluntary task-switching (compared to switching prompted by the experimenter) activated the rostrolateral prefrontal cortex, a brain region linked to executive control and multitasking (Benoit et al. 2012; Burgess et al. 2003; Gilbert et al. 2005, 2009). This analysis, however, was circumscribed to the moment of switching, and therefore it likely reflects the *decision* to switch, rather than the sustained activity that would reflect proactive maintenance and monitoring of the task goals (Braver 2012; Dosenbach et al. 2006). From this perspective, goal management could actually be studied in a blocked rather than event-related manner, because brain regions or networks involved in it should be tonically active during a block requiring this kind of monitoring, compared to blocks without this need (Braver 2012). In addition, block design has other advantages that are of interest when studying executively impaired populations, since it allows for shorter task duration and brain activity can be analyzed even if the subject has a poor task performance.

The aim of this work was to further validate the CMET as an ecologically valid tool to study the brain correlates of executive function and specifically goal management and task monitoring, with slight modifications to allow blocked analysis of brain activity. In this version of the CMET we compared blocks of voluntary switching with blocks of automated (performed by the computer) switching in a sample of healthy subjects. The voluntary switching blocks required maintenance of a higher task goal (switching games so approximately the same amount of time is dedicated to each) while playing each game to earn points. The automated switching blocks only required the subject to play the games –the switch occurred automatically and they just had to play whichever game was on screen. No time information was shown, so participants had to constantly monitor the task when voluntarily switching. We expected that the greater executive demands posed by this condition would drive an increase in the activity of the fronto-parietal and cingulo-opercular networks that have been identified in previous studies using classical executive paradigms. In a complementary analysis, we also tested whether the brain regions activated during the task showed synchronized activity during resting-state, thus forming stable, intrinsic functional networks.

Methods

Participants

Thirty-four healthy, right-handed subjects participated in the study. They were all required to be free from major medical or neurological illness, head injury with loss of consciousness, and drug or substance abuse or dependence in the last 12 months. Participants were also questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication and the Structured Clinical Interview for DSM-5 was also used to exclude current psychiatric disorders. One participant was excluded for this reason. Two other participants were excluded due to incidental findings in the MRI exploration and excessive head movement. The final sample included 31 subjects (15 male, 16 female) with a mean age of 34.06 years (SD = 13.02; range = 18–56). They all had an IQ in the normal range, as estimated by four subtests from the WAIS-III battery (Vocabulary, Similarities, Matrix reasoning and Block design; mean = 104.74, SD = 12.40, range = 81–134).

All participants gave written informed consent prior to participation. All the study procedures had been previously approved by the local research ethical committee and adhered to the Declaration of Helsinki. Participants received a gift-card as a compensation for their participation in the study.

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Task description

The CMET task was based on the version of the same paradigm developed by Cullen et al. (2016). In the task, participants were required to play four different games, which were presented sequentially in pseudorandom order. The games were all similar and involved moving an interactive element on the screen to the left or to the right (with their left or right index fingers) to earn points: in the first game (Car), the participant had to move a car to pick up fuel from the road; in the second (Catch), they had to move a tube to receive balloons that fell from the sky; in the third (Ball), they had to move a bar to keep a ball in movement and bouncing to the walls on the screen; in the last game (Brick), participants had to move a bar to use a ball to break bricks on the screen (Fig. 1).

Participants played these four games in two conditions: in the control condition (automatic switching), participants had to play the games and earn as many points as possible, with games switching automatically from one to another every 12 s until all games had been played once and the block ended (total block duration = 48 s). In the executive condition (voluntary switching), participants had to do the same, but in addition they had to decide themselves when to switch from one game to the other by pressing a button with their right thumb. They were instructed to try to play approximately the same amount of time each game, although no information about time played was available to them. Thus, the executive condition required participants to play the games to earn points but also to keep in mind that they needed to switch games regularly to be able to play all of them in each block (total block duration = 48 s). Four blocks of each condition were presented in alternating order, starting with the automatic condition to serve as a reference for switching time. Instructions were presented immediately before each block started for 3 s. Between blocks, a fixation cross was presented for 9 s. Total task duration was 8 min and 10 s.

Before scanning, participants underwent a practice session where they learned how to use the game controllers to play and switch games, but without any timing requirements. Although they were reminded that they should play each game for approximately the same time during the scanning session, they were free to practice for as long as they needed to get familiar with the games during the practice session.

Behavioral measures

Behavioral measures of interest included the amount of points earned, the total number of voluntary switches (similar to the behavioral outcome used in Cullen et al. (2016), of number of games played) and voluntary switches per block. We also calculated a measure of accuracy in terms of time played for each game: given that a perfect execution of the task would imply playing each game for 12 s in each voluntary switching block, we calculated the deviation from this optimal time as the total time (in seconds) exceeding 12 s per game played for each block (time underplaying and overplaying a game were complementary, so only overplaying was penalized to avoid counting time twice). For example, if in a given block and participant the amount of time dedicated to each game was 14 s, 12 s, 13 s and 9 s, total deviation from optimal playing time would be 3 s. The accuracy score was the sum of these deviations across the four blocks in the task, giving a range from 0 (perfect execution, played 12 s for all games in all blocks) to 144 (worse execution, no voluntary switches performed). This accuracy score represents the amount of

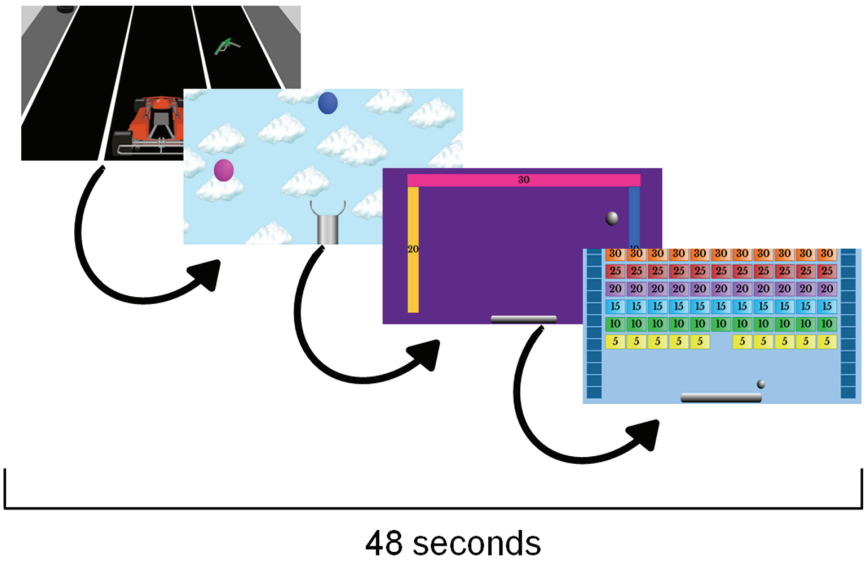

Fig. 1 Schematic view of the task. Participants sequentially played four games during each 48 s block. In the automatic switching condition, the game changed every 12 s without intervention of the participant. In the voluntary switching condition, the participant had to actively switch games by button press, with approximately the same frequency as in the automatic condition. No time information was shown during either condition

deviation from optimum playing time, as suggested by Hynes et al. (2015) and Cullen et al. (2016).

Image acquisition

Images were acquired with a 3 T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with 245 volumes and the following acquisition parameters: TR = 2000 ms, TE = 30 ms, flip angle = 70°, in-plane resolution = 3.5 × 3.5 mm, FOV = 238 × 245 mm, slice thickness = 3.5 mm, inter-slice gap = 0.75 mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. A resting-state sequence (8 min 52 s) was also acquired prior to the task, with 266 volumes and identical acquisition parameters to the task sequence. After the functional sequences, a high-resolution anatomical volume was acquired using a FFE (Fast Field Echo) sequence for anatomical reference and inspection (TR = 9.90 ms; TE = 4.60 ms; Flip angle = 8°; voxel size = 1 × 1 × 1 mm; slice number = 180; FOV = 240 mm).

CMET task image preprocessing and analysis

Preprocessing and analysis were carried out with the FEAT module included in the FSL (FMRIB Software Library) software (Smith et al. 2004). The first 10 s (5 volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm), co-registration and normalization to a common stereotactic space (MNI, Montreal Neurological Institute template). For accurate registration, a two-step process was used. First, brain extraction was applied to the structural image, and the functional sequence was registered to it. Then the structural image was registered to the standard template. These two transformations were used to finally register the functional sequence to the standard space. Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 7 mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

Statistical analysis was performed by means of a General Linear Model (GLM) approach. At the first level, the following regressors were defined: one for the effect of playing each game, independently of the condition, one for the effect of automatic switching (two seconds duration from switching time), and one for the effect of voluntary switching (two seconds prior plus two seconds after the switch, to capture both decision to switch and switching costs). Finally, a last regressor was added that coded for the voluntary switching (executive) blocks. Contrasts on this last regressor implicitly quantified changes in brain activity when playing the games in the executive condition relative to the control condition, while the effect of playing the games per se and the effect of game switches were controlled through the other regressors. Contrasts on this last regressor coding for voluntary vs. automatic switching differences were the contrasts of interest in our study. An additional contrast comparing voluntary > automatic switches was also examined (see details in Supplementary Materials). GLMs were fitted to generate individual activation maps for these contrasts and second level (group) analyses were performed within the FEAT module by means of mixed-effects GLMs (Beckmann et al. 2003). Statistical tests were carried out at the cluster level with a corrected p value of 0.05 using Gaussian random field methods. A threshold of z = 3.1, equivalent to an uncorrected $p < 0.001$, was used to define the initial set of clusters.

Resting-state image preprocessing and analysis

The preprocessing pipeline of resting-state images was identical to that used in previous work (Salvador et al. 2017). Briefly, this included (1) extraction of non-brain signal, (2) volume co-registration, (3) checking of movement levels (allowed thresholds were the same as those used in the task-based analysis), (4) scrubbing, (5) regression of movement parameters, (6) minimization of movement artifacts by regressing Independent Components with clear edge effects, (7) removal of linear and quadratic trends in time series, (8) non-linear normalization with intermediate fitting of individual T1 images and final fitting to the MNI template, (9) spatial filtering with a Gaussian kernel (σ = 3 mm), (10) regression of spurious trends characterized by the signal from a region of interest (ROI) in the lateral ventricles and six spherical ROIs located in white matter locations, and (11) temporal filtering with a low-frequency filter (0.01–0.1 Hz).

Connectivity maps were generated by building spheres with a 6 mm radius centered at the coordinates of interest, which were peaks of activation found in the CMET task. These spheres were used as seeds whose mean time-series (averaged over voxels within the sphere) were correlated with those from each other voxel in the brain. The resulting resting state correlation maps were thresholded at a value of 0.5, since it is defined as a large effect size for correlation analysis (Cohen 1992), to obtain connectivity maps showing the voxels with highest correlations with the seed. The same procedure was followed to generate resting state connectivity maps for the fronto-parietal and cingulo-opercular networks as described in Raichle (2011). In this case, we extracted the time series from the seeds forming the networks (taken from the coordinates listed in Raichle 2011), and their average was correlated with the time series of every voxel in the brain. Voxels with correlations above 0.5 were considered as members of the network. To quantify the similarity between the resting-state connectivity maps (either those derived from the

task-activation seeds or from the independently defined seeds in Raichle 2011) and the activation map from the CMET task, we calculated the Szymkiewicz–Simpson coefficient, also known as overlap coefficient (OC) (Vijaymeena and Kavitha 2016). The OC is a similarity measure that quantifies the overlap between two finite sets. In our setting it is given by a fraction in which the numerator is the area of the intersection between clusters contained in two different maps (i.e. the number of voxels that belong to the two maps simultaneously), and the denominator is the number of voxels in the smallest map (i.e. the map with smallest total cluster extent). The OC ranges from 0 to 1, with 1 occurring when one of the maps fully contains all the voxels of the other map and 0 corresponding to no overlap at all. Note, however, that even if the smaller map is fully contained within the larger map, leading to an OC = 1, it is quite probable that some regions in the larger map will not be included in the smaller map.

Results

Behavioral performance

Participants earned a mean of 3768.07 points (SD = 158.70, range = 3390–4015), which indicates good comprehension and performance of the games. If no actions were performed during the task, it was possible to earn up to 2280 points by chance; however, the score range in this sample is well above this value, indicating that participants were actively playing the games to earn points. Subjects scored an average of 1822 points (SD = 85.21, range = 1700–2040) in the automatic blocks and of 1942 points (SD = 124.23, range = 1665–2150) in the voluntary blocks, which indicates that the requirement to switch did not reduce their performance.

The mean total number of voluntary switches was 14.07 (SD = 5.13, range = 8–32). Subjects performed a mean of 3.52 voluntary switches per block (SD = 1.48, range = 1–11). This shows that all participants achieved at least one change per block, and that performance in the voluntary switching blocks was similar to the automatic ones (12 total switches, 3 per block). However, some participants performed more than the expected 12 switches. Given that they were not given a prespecified number of switches to perform during the task, but were instructed to dedicate approximately the same amount of time to each game, we considered that this type of performance did not indicate a misunderstanding of the instructions or executive problems, but rather that they were playing each game more than once per block. Thus, we calculated accuracy in terms of deviation from optimal playing duration as a more sensitive measure of performance. This measure, which reflects the difference between time actually dedicated to each game and the gold standard of 12 s per block, ranges from 0 to 144, with smaller values indicating better performance. In the present sample mean total accuracy was 27.19 (SD = 15.01, range = 7.96–74.59). There was a learning effect with greater deviation from optimal playing time in the first voluntary block (mean = 8.23 s, SD = 5.22) than in the last (mean = 5.83 s, SD = 3.67 s, $t_{(30)} = 2.82$, $p = 0.008$). Figure 2 shows this trend towards better accuracy as the task progressed.

As a complementary measure to study variability in switching times, we also calculated the coefficient of variation (CV) for the playing times during the voluntary condition. The CV is a measure of dispersion relative to the mean, and is defined as a ratio of the standard deviation to the mean of a distribution. Participants with smaller CVs in their playing times displayed a more stable performance pattern, while larger values indicated more variability. In our sample, the mean CV was 0.36 (SD = 0.13, range = 0.13–0.67).

None of the behavioral measures was significantly associated with age or IQ (total, verbal or manipulative) (all ps > 0.1).

Motion

Overall motion levels in the task were low. Total frame-wise displacement (FD) was on average 0.07 mm (SD = 0.05, range = 0.03–0.18). Mean maximum FD was 0.94 mm (SD = 0.73, range = 0.23–2.97). By conditions, the average FD in the automatic switching condition was 0.06 mm (SD = 0.05, range = 0.03–0.20), the same as in the voluntary condition (mean = 0.06 mm, SD = 0.04, range = 0.03–0.16). Motion was not different between conditions according to the Wilcoxon signed rank test ($p = 0.11$).

Imaging results

The executive condition (voluntary switching) was associated with increased activity in the lateral prefrontal cortex, spanning the DLPFC and the inferior frontal gyrus and anterior insula, especially in the right hemisphere, and in the right inferior parietal cortex, encompassing the supramarginal and angular gyri. Activity was also found in the bilateral frontal poles and in the dorsal ACC extending into the pre-SMA and SMA. We also observed marked activation of the left postcentral gyrus. Additional activation was found in the basal ganglia and thalamus, midbrain and cerebellum (Fig. 3, Table 1). On the other hand, activity in the ventral mPFC was reduced in the executive condition.

The comparison between voluntary and automatic switching events showed greater activation for voluntary switching in the middle and posterior cingulate, the precuneus, the left angular gyrus and the bilateral middle and superior temporal cortex (see details in the Supplementary Materials).

To further explore the link between brain activation and task performance, we defined six ROIs that corresponded to

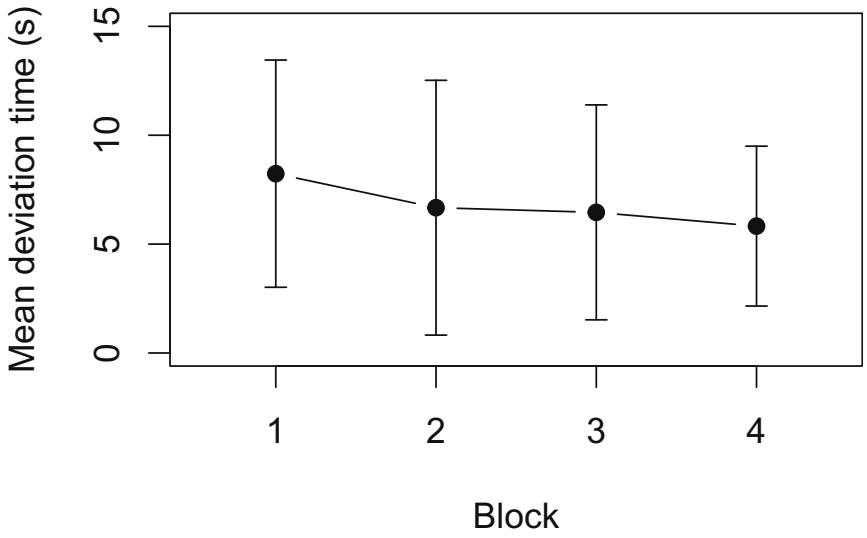

Fig. 2 Deviation from optimal playing time for each block. Error bars correspond to standard deviations

the peaks of maximum activation in the task in regions from the FPN and CON. ROIs were defined as 6 mm-radius spheres centered around activation peaks in the following regions (MNI coordinates in parentheses): right anterior insula (44, 18, −2), left anterior insula (−38, 22, −8), dorsal ACC (6, 26, 40), SMA (4, 14, 60), right DLPFC (34, 34, 26) and right inferior parietal cortex (48, −46, 42). We extracted mean parameter estimates from these ROIs for each subject and conducted Spearman's correlations with the timing accuracy measure (see Table 2). The right anterior insula showed a significant negative correlation with behavior (Fig. 4). Given that lower values in this measure mean better task performance, this result indicates that greater right anterior insula activity during the executive blocks is associated with better task performance. A similar trend was found for the right DLPFC and the right inferior parietal cortex, but without reaching statistical significance after multiple comparisons correction.

Resting-state analysis

Seeds for resting-state analysis were located in the same six CMET activation peaks used in the previous ROI analysis (i.e. right and left anterior insula, dorsal ACC, SMA, right DLPFC and right inferior parietal cortex). Figure 5 shows the resting state functional connectivity maps for each seed using a correlation threshold of 0.5 and their overlap with the activation map for the voluntary > automatic switching contrast, and the overlap coefficients that quantify the degree of similarity between the resting-state connectivity map and the task activation map.

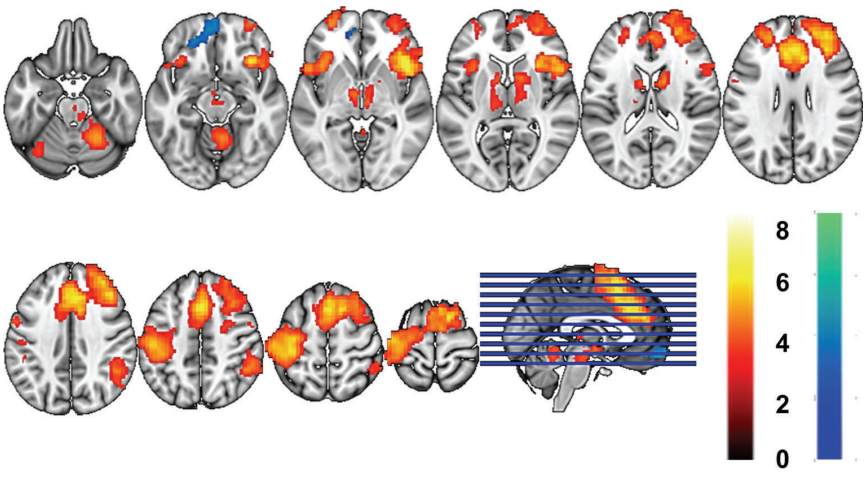

Fig. 3 Areas of increased (warm colors) and decreased (cold colors) activation in the voluntary switching condition compared to automated switching. Color bars depict Z values. Images are displayed in neurological convention (right is right)

Table 1 Brain regions activated in the CMET task

MNI coordinates						
Region	***x***	***y***	***z***	***Z***	**Cluster size**	***p***
Voluntary > Automatic						
SMA	4	14	60	6.48	18,427	<0.001
dACC	6	26	40	6.23		
	12	26	32	6.19		
Postcentral gyrus	−36	−28	58	5.97		
Precentral gyrus	−38	−16	62	5.93		
DLPFC	34	34	26	5.67		
Anterior insula (right)	44	18	−2	6.56	2473	<0.001
Inferior frontal gyrus	58	30	−6	4.06		
Anterior insula (left)	−38	22	−8	5.19	1006	<0.001
Inferior parietal cortex	48	−46	42	5.27	1324	<0.001
Supramarginal gyrus	54	−40	44	4.77		
Angular gyrus	48	−60	40	3.95		
Cerebellum (right)	24	−52	−26	4.85	3449	<0.001
Cerebellum (left)	−50	−64	−36	4.78	656	<0.001
Automatic > Voluntary						
Gyrus rectus	−2	56	−14	4.35	536	<0.001

ACC: Anterior cingulate cortex, SMA: Supplementary Motor Area, DLPFC: Dorsolateral prefrontal cortex.

The right anterior insula seed showed synchronized resting activity with surrounding insular and inferior frontal (opercular, orbitofrontal) cortex in both hemispheres, the dorsal ACC and SMA, the bilateral frontal poles and supramarginal gyri and a small area in the right premotor cortex. The resting connectivity map of the left anterior insula was essentially identical, with the exception that there was a correlation with the bilateral pallidum but no correlation with the premotor cortex, and the correlation with the right inferior parietal was smaller. However, these differences appear to be a result of thresholding, since lowering the correlation threshold to 0.4 involved the appearance of the premotor cortex associated with the left insula, and the pallidum with the right insula.

Similarly, the areas showing functional connectivity with the dorsal ACC included the right and left anterior insula, the neighboring SMA, the left and a small portion of the right frontal pole, and a small portion of the mid-cingulate cortex. For the SMA seed, functional connectivity was observed in the ACC, the left precentral gyrus, the left frontal pole, and the left thalamus. Functional connectivity with the bilateral inferior frontal cortex and anterior insula was also evident, but in a more lateral location than for the ACC. An additional area of functional connectivity with the SMA was observed in the right cerebellum.

The right DLPFC seed had functional connectivity with the left DLPFC and the right frontal pole, inferior frontal gyrus and anterior insula (in the right hemisphere but also with a small region of the left); also with the right inferior parietal cortex, the superior frontal gyrus, the ACC and the precentral gyrus. A very similar connectivity map was observed for the right inferior parietal seed, which in addition included the left inferior parietal cortex, but not the left DLPFC and inferior frontal cortex.

The overlap coefficients (OC) between the task-derived activation map (voluntary > automatic contrast) and resting-state connectivity maps showed the highest commonalities between the former and the ACC and SMA seed correlation maps. Here OC values were around 0.70 (see Fig. 5), meaning that approximately 70% of the connectivity maps for these two seeds (thresholded at a correlation value of 0.5) were contained within the task activation map. OCs were around 0.40 for the left and right insulae, 0.54 for the DLPFC and 0.44 for inferior parietal cortex. In general, Fig. 5 shows that the brain regions activated by the task seemed to roughly correspond to two intrinsic connectivity networks formed by these same regions at rest: one formed by the right and left anterior insula, ACC and SMA, and a second formed by the right DLPFC and right inferior parietal cortex.

To check the extent to which the regions activated by the CMET task corresponded with those associated to the FPN and CON described in Raichle (2011), we overlaid the connectivity maps of both brain networks, previously derived from the resting state data, onto the activation map from the voluntary > automatic switching contrast. As shown in Fig. 6 such overlay revealed a moderate degree of coincidence between both networks and voxels activated by the task, with OCs close to 0.30. However, there was also activation outside these canonical networks that included part of the medial superior prefrontal cortex (more extensively activated in the task than in the CON map), part of the right superior frontal cortex and the left motor cortex. At the same time, the connectivity maps included areas in the frontal cortex, posterior insula and inferior parietal that were not activated by the task.

Table 2 Correlation between ROIs mean activation and task performance

ROI	r_s	*p*
Right anterior insula	−0.627	<0.001*
Left anterior insula	−0.144	0.440
Dorsal ACC	−0.054	0.772
SMA	0.098	0.600
Right DLPFC	−0.377	0.038
Right inferior parietal	−0.396	0.028

*Significant at $p < 0.05$, Bonferroni corrected (uncorrected p/6 ROIs)

ACC: Anterior cingulate cortex; SMA: Supplementary Motor Area; DLPFC: Dorsolateral prefrontal cortex.

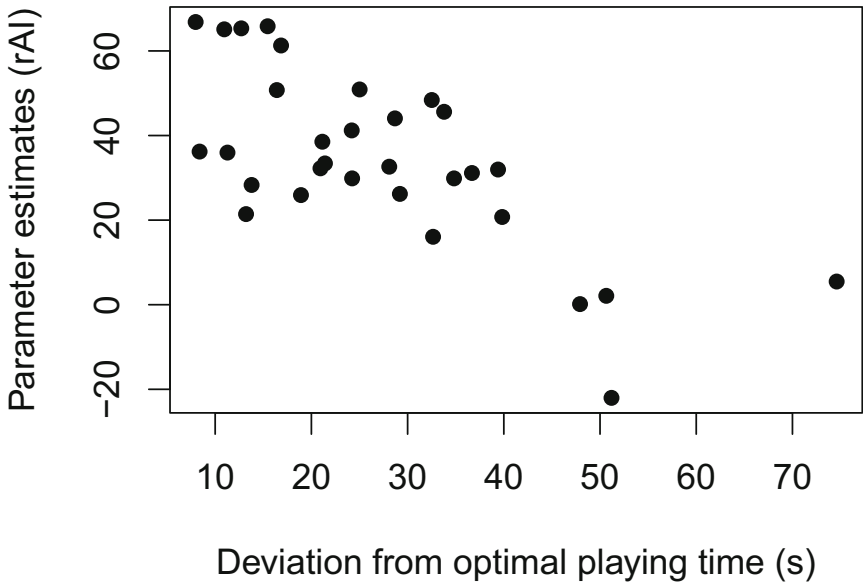

Fig. 4 Scatterplot depicting the association between behavioral performance and right anterior insula activity

Finally, we also examined the overlap between the resting-state networks derived from our task-seeds and the FPN and CON defined by independent seeds from Raichle (2011), which is illustrated in Fig. 7. Networks from the seeds in right and left anterior insula, ACC and SMA were overlaid onto the CON map, which showed that the anterior insula (especially the right) generated a connectivity map that was largely coincident with the independently defined CON network, with roughly a 90% overlap, while the networks from the ACC and SMA were much more restricted and included only part of the regions identified by the CON (OC was 0.42 for the ACC network and 0.51 for the SMA). The networks from the DLPFC and parietal cortex seeds were overlaid onto the FPN map, and both showed a large degree of overlap (0.80 for right DLPFC and 0.75 for right parietal cortex).

Discussion

The present study sought to validate an fMRI adaptation of the CMET to provide an experimental paradigm with greater ecological validity than classical tasks used to examine the imaging correlates of executive function. The task condition with greater executive demands was linked to increased activation in regions from top-down control and goal management functional networks: the FPN and the CON (Dosenbach et al. 2006, 2007, 2008). While these networks have been previously identified using classic paradigms (Lopez-Garcia et al. 2016) and with resting-state connectivity patterns (Allen et al. 2011; Dosenbach et al. 2007; Power et al. 2011; Yeo et al. 2011), we now show their involvement in a novel multi-element paradigm that is expected to reflect to a greater degree the brain activity patterns found in a daily-life situation. Thus, it holds the potential to characterize executive impairments that emerge in daily life in clinical populations.

We also showed that, when used as seeds in resting-state analysis, the regions identified by the CMET task form at least two functional networks which closely resemble the FPN and CON identified by resting-state analysis using independently defined seeds from previous literature (Raichle 2011). Importantly, we showed a substantial overlap between the task activation map and the FPN and CON identified in the same subjects, thus proving the involvement of these networks in the CMET task. A previous study by Sheffield et al. (2015) found that the integrity of these networks supports better cognitive ability, with a prominent role for the right anterior insula in the CON, which was the only region where participation as a hub within the network was found to be a significant predictor of cognitive ability. Similarly, the degree of activation of the right anterior insula was associated with task performance in our sample. The anterior insula is involved in many different attentional and executive tasks, including among others response inhibition (Swick et al. 2011), error processing (Menon et al. 2001), or interference resolution (Eckert et al. 2009). This ubiquity has led to assign the anterior insula a role in domain-general attentional control (Nelson et al. 2010). The CON, including the anterior insula, has been proposed as sustaining a task control system that maintains stable task-set representations (Dosenbach et al. 2008), an interpretation that aligns well with our results both in terms of brain activation and brain-behavior correlations. At the same time, our resting-state results support the view of the anterior insula as a functional hub that regulates between-network interactions. Resting-state connectivity maps were highly similar for the

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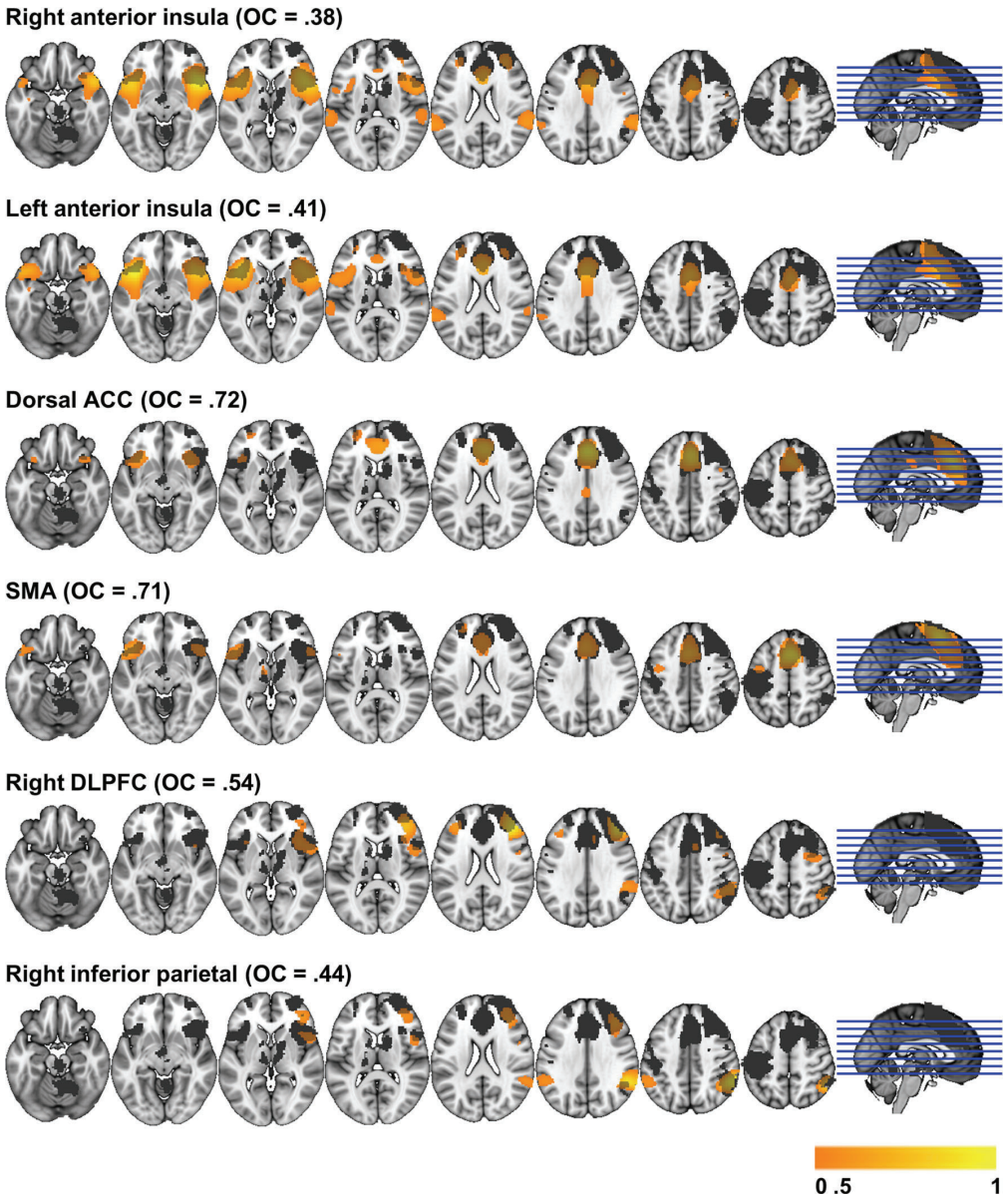

Fig. 5 When resting-state functional connectivity maps for the six seeds identified in the CMET task (orange-yellow) are overlaid onto the activation map for the voluntary > automatic switching contrast (grey) a high degree of anatomical agreement is observed between resting and task related activity (overlap coefficients are shown in parentheses). Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right)

regions within each of the proposed networks –the right and left insulae, dorsal ACC and SMA as the CON, and the DLPFC and inferior parietal cortex as the FPN. However, the anterior insula also appeared (albeit attenuated) in the connectivity maps of the DLPFC and inferior parietal cortex, consistent with a view of this area as a between-network connection node (Cai et al. 2016). Moreover, the CON network derived from Raichle's (2011) seeds actually included some portions of the DLPFC and inferior parietal cortex, and these were also apparent in our resting-state networks derived from the right and left insula seeds from the task, with a large overlap between them, while the CON estimated from the ACC and SMA seeds was restricted to the medial prefrontal regions (ACC/SMA) and anterior insula, with much smaller

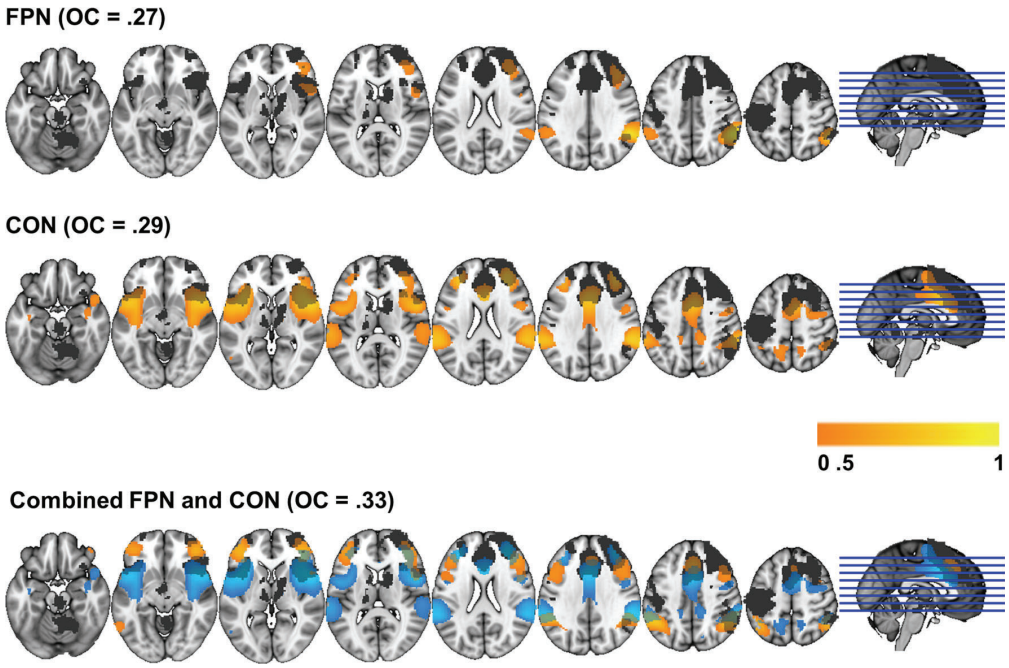

Fig. 6 Resting state functional connectivity maps for the FPN and CON as defined by Raichle (2011) (orange-yellow) overlaid onto the activation map for the voluntary > automatic switching contrast (grey) reveal a considerable degree of anatomical coincidence, clearly suggesting the involvement of both networks in the execution of the task (overlap coefficients are shown in parentheses). Lower row shows both networks simultaneously in yellow (CON) and blue (FPN) to illustrate the overlap between the task activation map and the combined regions of these two networks. Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right)

participation of dorsolateral or rostrolateral prefrontal areas. This is also indicative of the anterior insula having functional connectivity with a wide network of brain regions that may include areas outside the "canonical" CON. In fact, some of the regions identified by resting-state connectivity were not involved in the task, as in the case of the posterior insula in the CON or the left hemisphere regions of the FPN. In the latter case, lowering the statistical threshold showed activity in the left DLPFC and parietal cortex, although executive tasks sometimes show different roles for the right and left FPN (Fassbender et al. 2006; Zhang and Li 2011). In the CON case, results might be showing modularity within the network, with only part of the CON being engaged in the executive task.

The pilot validation of this task showed activation in the rostrolateral prefrontal cortex in a small sample of healthy subjects (Cullen et al. 2016). Although we have applied a different analysis strategy (blocked vs. event-related), we have also observed activity in this region. The rostrolateral (anterior) prefrontal cortex has shown in previous studies functional connectivity with the ACC and anterior insula, and has been proposed to provide specific representations of plans, subgoals, rules and/or strategies for complex tasks (Dosenbach et al. 2007), which is consistent with its activation in both studies. Moreover, our resting-state analysis also showed that the anterior insula and the dorsal ACC were functionally coupled with a region of the anterior frontal cortex (frontal pole) very close to the rostrolateral prefrontal activation identified in Cullen et al. (2016), supporting the association of this region with the CON. Note, however, that activation of this region in the executive condition extended beyond the area identified by the resting-state network. We might speculate that this region, although not canonically part of the CON or FPN, is linked to these networks and, as shown by previous studies, plays an important role in task control and goal management. On the other hand, the comparison between voluntary and automatic switching events (following the analysis approach used in Cullen et al. 2016) did not show activation in this region or in others usually linked with executive function, but it activated regions of the visual cortex default-mode network instead. However, these results should be taken with caution since the task was not designed for an event-related analysis.

An unexpected region of activation in our results was the left motor and premotor cortex. Activation differences between conditions in motor areas were not expected, since both conditions involved similar motor responses with the left and right hands. In the voluntary condition, however, switches were performed by pressing a button with the right hand.

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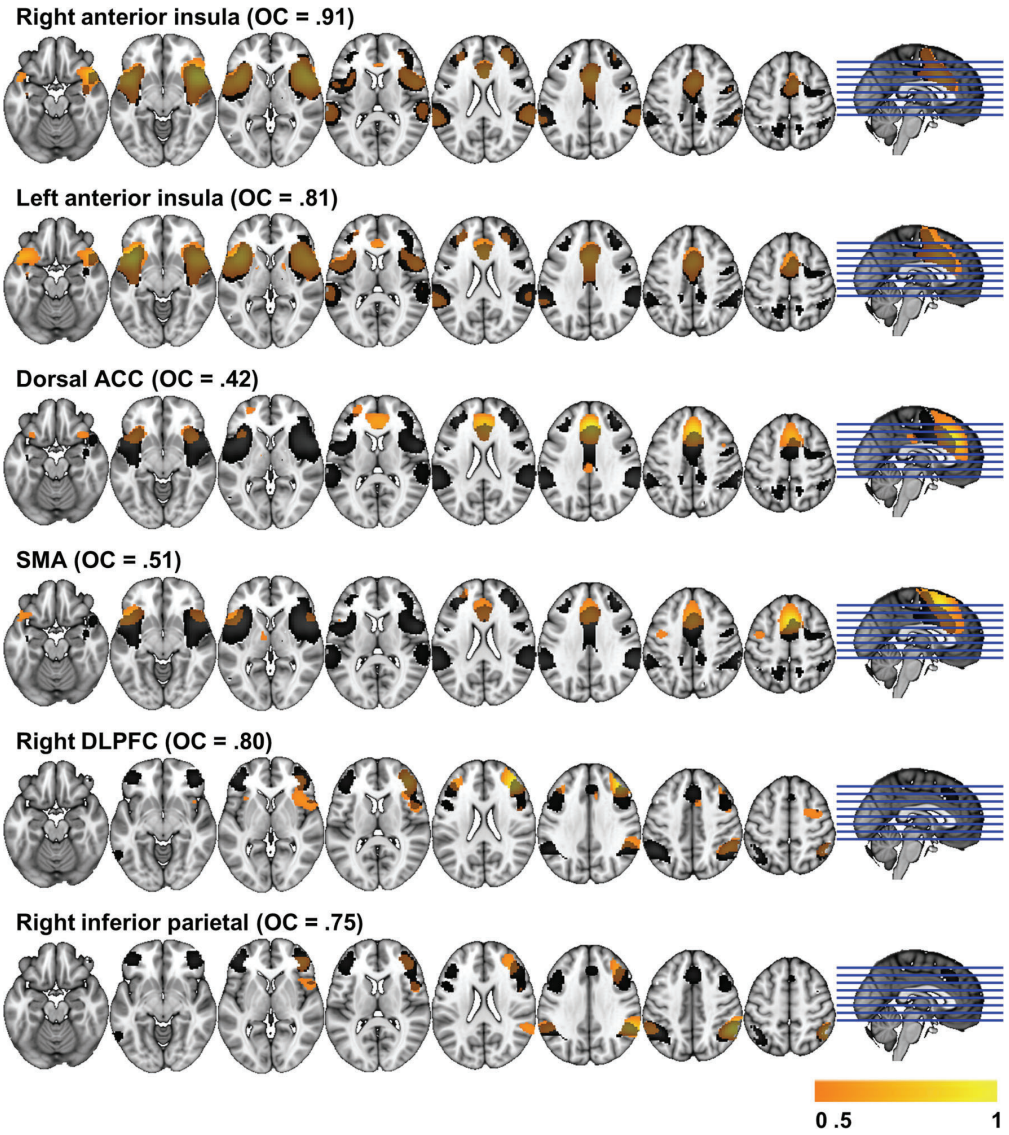

Fig. 7 Resting-state functional connectivity maps derived from the seeds identified by the executive task overlaid onto the resting-state connectivity maps for the CON (for the anterior insula, ACC and SMA maps) and FPN (for DLPFC and inferior parietal cortex) from Raichle (2011), thresholded at a correlation value of 0.5. The large degree of overlap demonstrates the agreement between the two groups of networks (overlap coefficients are shown in parentheses). Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right)

While this could explain the increased left motor activity in voluntary switching blocks, brain activity circumscribed to the moment of switching should have been captured by the GLM applied in the first-level analysis, which included a regressor coding for switches in each condition. A possible reason for this finding is that left motor/premotor activity spread beyond the moments of switching, perhaps reflecting motor planning or preparation before performing the switch. Another unexpected result was the reduction of medial prefrontal activity in the executive condition. This reduction might reflect the inhibition of the default-mode network, given that the medial prefrontal cortex is a relevant node of this network and shows reduced activation when task difficulty increases (Singh and Fawcett 2008).

The main difference between the present CMET version and the original is that, in the present study, the control condition involved switches made by the computer, instead of prompted and then performed by the participant. However,

this modification does not alter the condition of interest, which still requires to manage two goals (play the games and switch) while only one goal is maintained in automatic switching (play the games), and ensures identical visual stimulation in both conditions. Despite modifications, the task still fulfils the same Burgess' (2000) characteristics for a multitasking situation as the original: several tasks must be completed one at a time, it requires acting on delayed intentions, performance is self-determined, and there is no immediate feedback (Cullen et al. 2016). Also keeping with the original, the CMET is brief, with minimal instructions, a simple interface, and suitable for fMRI. The block analysis that we propose is also interesting to study populations with executive impairments, who are likely to perform fewer switches and may not achieve enough estimations to have a reliable BOLD signal for an event-related analysis. Our behavioral analyses included not only the number of switches, but also an additional measure of deviation from optimum playing time that Cullen et al. (2016) already recommended, and a measure of variability in task performance. The addition of these measures refines the analysis of behavioral performance, as they avoid ceiling effects which are likely to appear in healthy subjects, and might capture altered switching patterns in clinical populations (e.g. switching many times in one block and no times in the others). As in Cullen et al. (2016), none of the behavioral measures correlated with IQ, further adding discriminant validity to the task. However, the relationship between general intelligence and CMET performance should also be explored when using this task in clinical populations or samples with higher age and IQ variability, as associations may arise when the range of these measures or variation in task performance increase. A limitation of the present work is that no other goal management measures were used for assessing convergent validity. However, our sample involved healthy subjects with no cognitive impairment, who were expected to perform at ceiling in tasks like the MSET. In addition, previous work already showed good convergent validity for the CMET with other goal-management tests in clinical populations (Cullen et al. 2016; Hynes et al. 2015).

In summary, the CMET has shown its ability to elicit activation in the brain regions that belong to well-established functional networks involved in executive function and also identified in resting-state, becoming a useful research tool for studying the neurobiological correlates of executive deficits in neuropsychiatric populations. Future studies may use it to provide an ecological assessment of executive functions in neuropsychiatric and neurological disorders, and capture deficits in goal management and its associated brain activity that might not be apparent in strongly structured tasks like the classical attention paradigms.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11682-020-00425-0.

Acknowledgments This work was supported by the CIBERSAM and the Catalonian Government (2014-SGR-1573 and 2017-SGR-1271 to FIDMAG). Also by a grant from the Plan Nacional de I + D + i 2013–2016: Juan de la Cierva-formación contract (FJCI-2015-25278 to PF-C). And by the Instituto de Salud Carlos III, co-funded by European Union (ERDF/ESF, "Investing in your future"): Miguel Servet Research contracts (CPII13/00018 to RS and MS10/00596 to EP-C), and Research Project Grants (PI14/01151 to RS, PI14/01148 to EP-C and PI14/01691 to PM).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Comité de Ética en Investigación Clínica FIDMAG Hermanas Hospitalarias) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Apathy-avolition symptoms and executive dysfunction in schizophrenia: fMRI study with ecological assessment of goal management

Goal 2. Assessment of the neural correlates of executive dysfunction in schizophrenia with fMRI and CMET task, comprising case-control comparison of mean activation patterns, correlation with negative symptoms severity, and the evaluation of intersubject variability in brain activation during the task.

Apathy-avolition symptoms and executive dysfunction in schizophrenia:

fMRI study with ecological assessment of goal management

ABSTRACT

Executive dysfunction has been identified as a core feature of schizophrenia disorder, associated with brain abnormalities in high-cognitive networks. It is though that negative symptoms, particularly motivational deficits and apathy-avolition, are associated with executive dysfunction, given the similarity of symptoms with patients suffering from prefrontal lesions. However, brain imaging evidence supporting the link between executive dysfunction and negative symptoms have been limited, probably because the cognitive tasks used to assess executive functions usually neglect the multitasking and open-ended nature of real-life situations, failing to capture real-world difficulties of patients with schizophrenia. In the current study, we assessed brain abnormalities associated with executive dysfunction with functional MRI and the Computerized Multi Elements Test (CMET), a task designed to assess goal management and task monitoring in an ecological way, mimicking the multifaceted cognitive demands of real-life situations. We compared the activation pattern of chronic patients with schizophrenia and healthy controls matched by age, sex and premorbid IQ. In addition, we explored within-group consistency of brain activation across subjects, and statistically tested whether patients exhibited abnormal patterns of intersubject variability. We found that goal management deficits in schizophrenia were associated with a pattern of hypoactivation in core regions of cingulo-opercular (salience) and posterior regions of the frontoparietal (central executive) networks, and also abnormalities in intersubject variability in patients. Variability analysis also revealed that brain activation in superior frontal gyrus was modulated by the severity of apathy-avolition symptoms, supporting the hypothesis of executive dysfunction of the motivation domain of negative symptoms.

INTRODUCTION

Executive dysfunction is a core feature of schizophrenia disorder (139,147). It is already present in medication naïve patients with first-episode psychosis and first-degree relatives (122,150,151), and remains relatively stable after the psychotic outbreak (195). In fMRI studies, executive dysfunction has been consistently associated with hypoactivations in frontoparietal (central executive) and cingulo-opercular (salience) networks, although abnormal hyperactivations has also been reported in other prefrontal regions, which might reflect compensatory responses (19).

It is though that negative symptoms in schizophrenia, particularly motivational deficits and apathy-avolition, are associated with executive dysfunction, given the similarity of symptoms with patients suffering from lesions in dorsomedial prefrontal or anterior cingulate cortices (150). Structural and functional abnormalities in prefrontal cortex have been associated with negative symptoms (68,167), although brain imaging evidence supporting the link between executive dysfunction and negative symptoms have been sparse (72).

Most of these brain imaging studies assessed executive functions by means of neuropsychological tests and cognitive tasks that measure its different components separately, e.g., planification and anticipation, initiation of activity, self-monitoring, working memory, mental flexibility and problem solving, among others (108,171). However, such instruments usually neglect the multitasking and open-ended nature of real-life situations, failing to capture real-world difficulties of patients with schizophrenia (174–176). It led to a growing interest in the development of more ecological instruments (170,177,178), but the adaptation of executive tests into an fMRI environment has not been easy due to movement constraints and fMRI timing requirements. One of these attempts led to the development of the Computerized Multi Elements Test (CMET) (179,180), which has been recently validated and adapted to be used in clinical populations with executive dysfunction (193,196). CMET task is an scanner friendly adaptation of the Modified Six Elements Test (MSET), a neuropsychological test designed to assess the self-regulation of behavior and goal management (178), able to capture deficits in task monitoring and goal neglect in first-episode (149,181) and chronic patients with schizophrenia (182,183).

Another focus of recent interest in the field of psychiatry is the identification of biologically homogeneous subtypes of patients with schizophrenia (26,197). The characterization of intersubject variability of brain function might help to identify such biological subtypes (45,46). Common abnormalities shared across the disorder might be reflected as reduced interindividual variability, while heterogeneous underlying alterations could be detected by its increased variability across patients (48,49). Previous fMRI studies reported higher interindividual variability in resting-state networks in patients with schizophrenia (189–191,194). However, it remains unclear how resting-state abnormalities reported in intersubject variability will be translated into task-evoked brain activity. Will brain abnormalities underlying executive dysfunction be homogeneously distributed across subjects? Or, on the contrary, will we detect subgroups of patients based on the localization and extension of brain abnormalities?

In the current study, we addressed these questions by means of the CMET task and functional MRI in a sample of chronic patients with schizophrenia and healthy controls matched by age, sex, premorbid IQ and head motion. In addition to the assessment of brain activation associated with goal management, and its association with negative symptoms severity, we also explored within-group consistency across subjects using overlap maps (198). Finally, we statistically tested whether patients exhibited brain abnormalities in intersubject variability by means of subject-specific deviation maps from within-group mean brain activation (199).

METHODS

Participants

The patients' sample consisted of 90 right-handed patients with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder recruited from four different hospitals in the Barcelona area (Benito Menni CASM, Hospital de Sant Rafael, Hospital Sagrat Cor de Martorell, Hospital Mare de Déu de la Mercè). Diagnosis was made by means of clinical interview and review of case notes. Patients were excluded if they (a) were younger than 18 or older than 65 years, (b) had a history of brain trauma or neurological disease, and (c) had shown alcohol/substance abuse within 12 months prior to participation. Patients with a current IQ below 70 were also excluded from the study. All patients were taking antipsychotic medication.

The control sample consisted of 30 right-handed healthy individuals recruited from non-medical staff working in the hospital, their relatives and acquaintances, plus independent sources in the community. They were selected from a larger cohort of healthy subjects so as to be matched to the patients for age, sex and premorbid IQ, as estimated using the Word Accentuation Test (Test de Acentuación de Palabras, TAP) (200,201), requiring the pronunciation of low-frequency Spanish words whose accents have been removed. The controls met the same exclusion criteria as the patients. Controls were also excluded if they had a history of mental illness and/or treatment with psychotropic medication, or a history of mental illness in a first-degree relative.

All participants gave written informed consent prior to participation. All the study procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Healthy controls received a gift-card as a compensation for their participation in the study.

Clinical assessment

Symptoms severity was rated using the Positive and Negative Syndrome Scale (PANSS) (202). Based on Chen and colleagues (203), we clustered PANSS items in the following factors: Negative factor (blunted affect, emotional withdrawal, poor rapport, apathetic social withdrawal, low spontaneity / flow, mannerisms and posturing, motor retardation), positive factor (delusions, hallucinations, grandiosity, unusual thought content), affective factor (suspiciousness / persecution, somatic concern, anxiety, guilt feelings, tension, depression, active social avoidance) and cognitive factor (conceptual disorganization, hyperactivity / excitement, hostility, difficulty in abstract thinking, stereotyped thinking, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation).

We additionally rated negative symptoms using the Clinical Assessment Interview for Negative Symptoms (CAINS) (74,204). Scores on individual CAINS items are summed to give an overall score, plus two subscale scores: motivation and pleasure (CAINS-MAP, 9 items), focuses on lack of motivation and anhedonia, and expressivity (CAINS-EXP, 4 items) rates lack of facial expression, expressive gestures, prosody and amount of speech. Current IQ was estimated using four subtests from the WAIS-III battery (Vocabulary, Similarities, Matrix reasoning and Block design);

Task description

The Computerized Multiple Elements Test (CMET) (180) requires subjects to sequentially play four different video-type games presented in pseudorandom order (see Figure 1). The games are all similar and involve moving an interactive element on the screen to the left or to the right (with their left or right index fingers) to earn points: in the first game (car), participants have to move a car to pick up fuel from the road; in the second (catch), they have to move a tube to receive balloons that fall from the sky; in the third (ball), they have to move a bar to keep a ball bouncing off walls; in the fourth (brick), they have to move a bar to use a ball to break bricks. The four games are played in two conditions: in the control condition (automatic switching), the games switch automatically from one

to another every 12 seconds until all games have been played once. In the executive condition (voluntary switching) participants have to decide when to switch from one game to the other by pressing a button with their right thumb, with the aim of playing all of them in each block. In this condition the subjects are instructed to divide their time equally to spend approximately the same on each game, although no time information is shown in either condition.

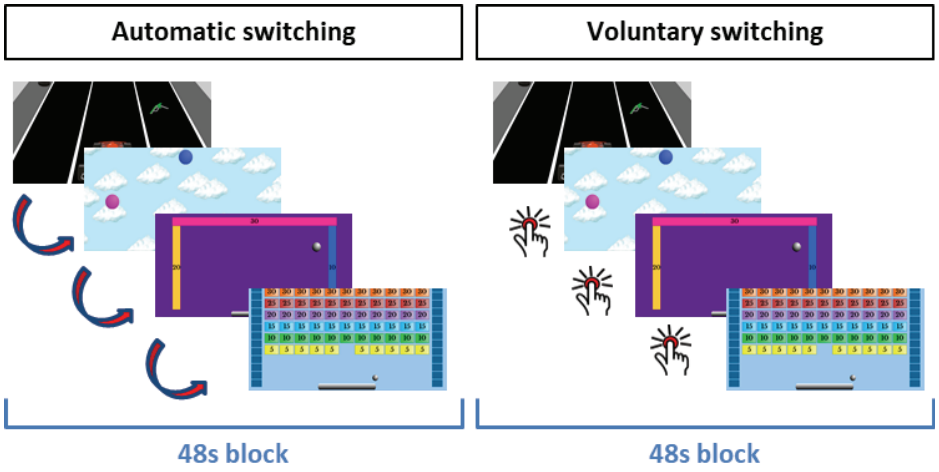

Figure 1. Schematic view of the CMET. Participants sequentially play four games during each 48s block. In the automatic switching condition, the game changes every 12s without the intervention of the participant. In the voluntary switching condition, the participant has to actively switch games by button press, with approximately the same frequency as in the automatic condition. No time information is shown during either condition.

Stimuli were presented via MRI-compatible goggles (VisuaStim, Resonance Technology), and participants performed the task with an MRI-compatible response system (ResponseGrips, NordicNeuroLab). Four blocks of each condition were presented in alternating order, starting with the automatic condition. Instructions were presented immediately before each block started for 3s and indicated whether the subsequent block corresponded to the automatic or the voluntary condition. Between blocks, a fixation cross was presented for 9s. Total task duration was 8 minutes and 10 seconds. Before scanning, participants underwent a practice session where they learned how to play and switch games.

Behavioral measures

Deviation from optimal playing time was used as a metric of behavioral performance, consisting of the sum of deviations from the ideal strategy in the voluntary switching condition of playing each game for 12s (time underplaying and overplaying a game were complementary, so only overplaying was penalized to avoid counting time twice). The deviation from optimal playing time was the sum of these deviations across the four blocks in the task, giving a range from 0 (perfect execution, played 12 s for all games in all blocks) to 144 (worse execution, no voluntary switches performed). From now on, to facilitate the interpretation of the results, we defined 'task performance' as the negative of the deviation time.

Image acquisition and preprocessing

Images were acquired with a 3T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with 245 volumes and the following acquisition parameters: TR = 2000ms, TE = 30ms, flip angle = 70°, in-plane resolution= 3.5 × 3.5mm, FOV = 238 × 245mm, slice thickness = 3.5mm, inter-slice gap = 0.75mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. We also acquired a high-resolution anatomical volume with a FFE (Fast Field Echo) sequence for anatomical reference and inspection (TR = 9.90ms; TE = 4.60ms; Flip angle = 8°; voxel size = 1 × 1mm; slice thickness = 1mm; slice number = 180; FOV = 240mm).

Preprocessing and analysis was carried out with the FEAT module included in the FSL (FMRIB Software Library) software (205). The first 10 seconds (5 volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm), co-registration and normalization to a common stereotactic space (MNI, Montreal Neurological Institute template). For accurate registration, a two-step process was used. First, brain extraction was applied to the structural image, and the functional sequence was registered to it. Then the structural image was registered to the standard template. These two transformations were used to finally register the functional sequence to the standard space. Before group

analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 5mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

Analysis

The analysis was organized in three main steps corresponding to the main goals of this study: 1) voxel-wise group comparison of activation maps of patients vs controls in the main contrast of interest voluntary switching > automatic switching, and correlation analysis with negative symptoms' scores, 2) voxel-wise assessment of within-group intersubject variability, and 3) ROI analysis to evaluate the association between patients' abnormalities in mean activation and interindividual variability.

Group activation maps

General linear models (GLM) were used to obtain activation maps in the two groups. At the first level, we defined a regressor for each condition: one for automatic switching blocks and one for voluntary switching blocks (fixation periods were not modeled and acted as implicit baseline). The contrast of interest was voluntary switching > automatic switching, to identify regions of increased sustained activation when playing the games with goal management demands. Second level (group) analyses were performed within the FEAT module by means of mixed-effects GLMs (206), to obtain mean activation maps for each group. For the group comparison, we performed two-sample t-tests modelling within-group variance separately for patients and controls. Correlation analyses were performed with negative factor, CAINS total and CAINS subscales Map (motivation and pleasure) and Exp (expressivity deficits).

All statistical tests were carried out at the cluster level with a corrected p value of 0.05 using Gaussian random field methods. The default threshold of z > 3.1 was used to define the initial set of clusters. High-level statistical analyses

included age, sex, premorbid IQ, current IQ and head motion, i.e. mean framewise displacement (207), as nuisance factors. Images depicted were created using MRIcron (208).

Intersubject variability

Interindividual variability in brain activity was analyzed by means of threshold-weighted overlap maps (198) and subject-specific deviation maps from within-group mean activation (199).

Overlap maps (OM) quantify the proportion of subjects with active voxels over a wide range of statistical thresholds (198). For each voxel, we created a histogram of the proportion of subjects with this voxel active (y-axis), relative to the statistical threshold (x-axis), ranging from $z_{min} = 0$ to $z_{max} = 3.1$ in steps of 0.1. Then, we applied a simple linear function that increases with threshold as a weighting function, in order to assign more weight to individual effects at higher statistical thresholds, and to make the area of the weighted histogram within the range [0 1]. Finally, we computed the area under the curve, to get one value per voxel. OM values close to 1 indicates a very consistent activation across subjects, while lower values in OM could arise from all subjects with active voxels below a certain threshold, or from a subset of subjects with active voxels at any threshold, suggesting the existence of subgroups. To discriminate between these two scenarios, we recomputed the overlap maps with lower z_{max}, since the former case would return higher OM values, while the latter would return similar OM values (see Seghier and Price (198); for a detailed description of the method).

Individual maps of deviation (199) were created by subtraction of the mean within-group activation z-map (second-level) from the individual z-map (first-level) for the contrast of interest voluntary vs automatic switching. We computed the absolute value of the subtraction, in order to avoid that deviations of equal magnitude but opposite direction cancel out each other. Then, we performed a group comparison and within-group correlation with task performance, through permutation tests with 5000 iterations (randomize in FSL). Voxels with $p < 0.05$ were considered significant after correcting for multiple comparisons with threshold-free cluster enhancement (209). Since we were interested in the variability in brain activity associated with the task, we restricted the permutation

test to those voxels that showed a significant within-group activation. In addition, we also performed a supplementary whole-brain voxel-wise analysis. Group comparison and correlation with task performance were carried out with age, sex, premorbid IQ, current IQ and head motion as nuisance factors. Correlation analyses in patients' group also included antipsychotic medication as a covariate.

ROI analysis

In order to assess the association between patients' abnormalities in mean activation and deviation (see results below), we performed the following region-of-interest analyses. In significant clusters where we observed an abnormal activation in patients, we carried out a Spearman's correlation between activation and behavioral performance in each group, and a group comparison of deviation with a Wilcoxon test. To control for confounding effects, before performing the analyses, we calculated the residuals from a linear model with the variable of interest (activation) as dependent variable and age, sex, premorbid IQ (Word Accentuation Test), current IQ (WAIS-III) and head motion as independent variables. Then we used the residuals of the linear model for the group comparison and correlations.

In significant clusters where we observed an abnormal interindividual variability (deviation) in patients, we performed a correlation between deviation and behavioral performance in each group, and a group comparison of activation, as described above. Additionally, in the clusters of increased deviation in patients, we proceed as follows. For each cluster, we created three subgroups of 30 patients with deviation values a) above the 66% quartile (high deviation subgroup), b) between 66% and 33% quartiles (middle deviation subgroup), and c) below 33% quartile (low deviation subgroup). Then, we compared mean activation of each group with healthy controls with a Wilcoxon test. Finally, we compared negative symptoms' scores between subgroups with Wilcoxon tests. All group comparisons were performed after regressing out the effect of age, sex, premorbid IQ, current IQ and head motion. We corrected for multiple comparison for all the ROI analyses using False Discovery Rate (210).

RESULTS

The sample consisted of 90 patients (73 with schizophrenia and 17 with schizoaffective disorder). 18 of the patients were on acute or subacute wards, 8 in long-stay rehabilitation settings, 11 in community care settings, 10 in daycare settings and 43 were outpatients. All patients had chronic illnesses (duration > 2 years). Tables 1 and 2 show demographic and clinical data, respectively. Patients did not differ significantly from healthy controls in age, sex, premorbid IQ or head motion; however, they had a significantly lower current IQ than healthy controls.

Table 1. Demographic data.

	SZ (n=90)	**HC (n=30)**	**Stats**
Sex M/F	56/34	16/14	X^2=0.42, p=0.52
Age	42.4 ± 10.82	39.13 ± 13.82	W=1212, p=0.41
Estimated premorbid IQ (TAP)	98.79 ± 8.25	101.3 ± 8.93	W=1602, p=0.13
Current IQ (WAIS-III)	93.49 ± 12.89	103.7 ± 11.42	W=1952, p=0.0003
Head motion (mean FD)	0.0593 ± 0.019	0.0550 ± 0.018	W=1139, p=0.202

FD, framewise displacement; HC, healthy controls; SZ, schizophrenia patients; X^2, chi squared statistic; W, Wilcoxon rank sum test.

Table 2. Clinical data.

	SZ (n=90)
PANSS Total score	54.42 ± 14.29
Negative factor	15.43 ± 7.07
Positive factor	7.51 ± 3.22
Cognitive factor	12.9 ± 4.83
Affective factor	18.58 ± 4.92
CAINS Total score	22.4 ± 10.68
CAINS-MAP	18.19 ± 7.89
CAINS-EXP	4.21 ± 4.15
Duration of illness (years)	18.13 ± 11.34
Antipsychotic dose (CPZ eq)	419.21 ± 304.98

CPZ eq, chlorpromazine equivalence; SZ, schizophrenia patients.

Behavioral results

Task performance was not normally distributed and so group comparisons and correlations were carried out with nonparametric tests (Mann-Whitney U and Spearman correlation). Task performance was significantly better in controls than in patients (deviation time: HC median = -14.47, IQR = 9.36; SZ median = -60.56, IQR = 59.46; U = 290, $p < 0.001$). In healthy controls, task performance was not significantly correlated with age, sex, premorbid or current IQ. In patients (Figure 2), task performance showed a positive correlation with premorbid (rho = 0.25) and current IQ (rho = 0.35), and a negative correlation with age (rho = -0.29), head motion (rho = -0.34) and cognitive factor (rho = -0.34). When the effects of age, sex, premorbid and current IQ were regressed out from task performance and clinical scores, task performance was only correlated with the cognitive factor (rho = -0.25) (Figure 3). Correlations described above are those with an uncorrected $p < 0.05$, since we presented them only for descriptive purposes.

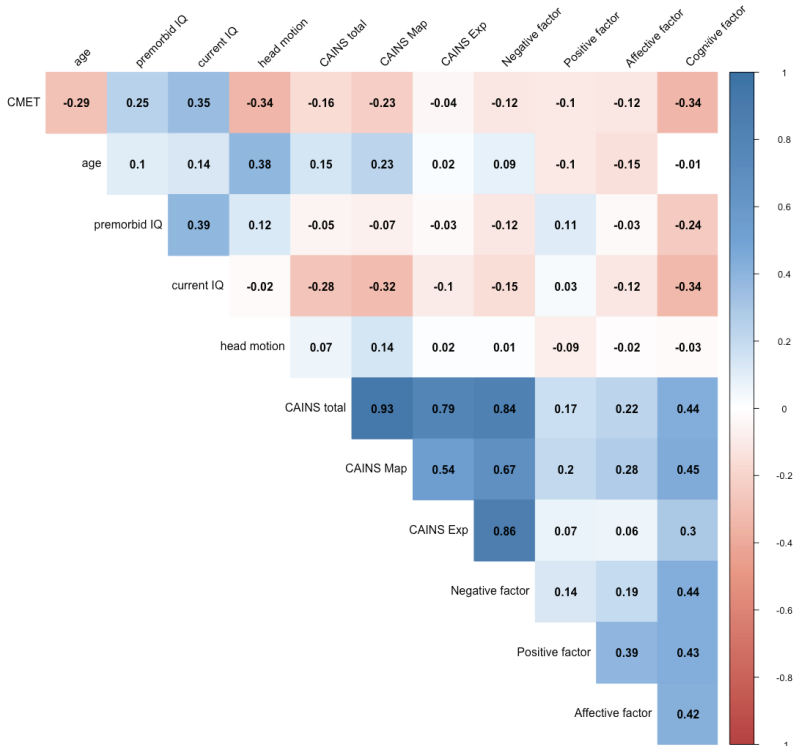

Figure 2. Correlations between task performance, demographics and clinical data of patients with schizophrenia. Spearman's Rank correlation coefficients are shown. * uncorrected $p < 0.05$

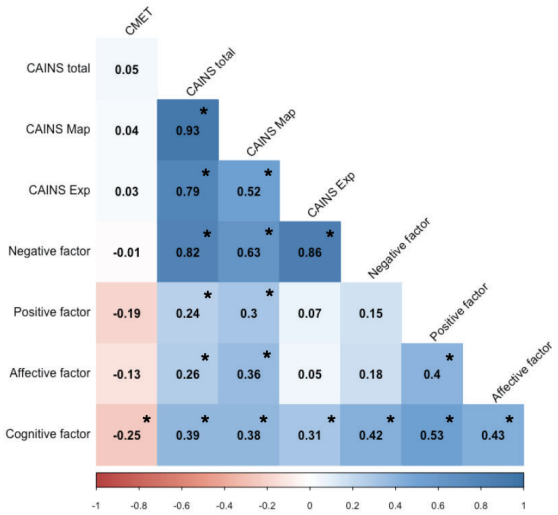

Figure 3. Correlations between task performance and clinical symptoms severity after controlling for age, sex, premorbid IQ and current IQ, in patients with schizophrenia. Spearman's Rank correlation coefficients are shown. * uncorrected $p < 0.05$

Activation findings

Both groups showed a similar pattern of activations in the contrast of interest (voluntary > automatic switching) (Figure 4A), comprising middle frontal gyrus (right > left), superior frontal gyrus (midline), frontal pole (right > left), as well as the bilateral frontal operculum and anterior insula. There was also an activation in left pre-postcentral, bilateral angular gyri, posterior cingulate, and bilateral middle temporal gyri (for further details see Supplementary Table S1). Regarding deactivations (voluntary < automatic switching), both groups showed a cluster in medial prefrontal cortex, and patients showed additional clusters in left lateral occipital and inferior temporal gyrus. (See Figure S1 and Table S2 in Supplementary Material).

Voxel-wise group comparison (Figure 4D, red) revealed clusters of significantly reduced activation in the patients in bilateral angular gyri / lateral occipital (right: $z_{max} = 6.45$, 399 voxels; left: $z_{max} = 4.03$, 232 voxels), paracingulate /

anterior cingulate cortex (z_{max} = 4.04, 144 voxels) and right anterior insula / frontal operculum (z_{max} = 4.32, 135 voxels). We found no clusters of increased activation in patients.

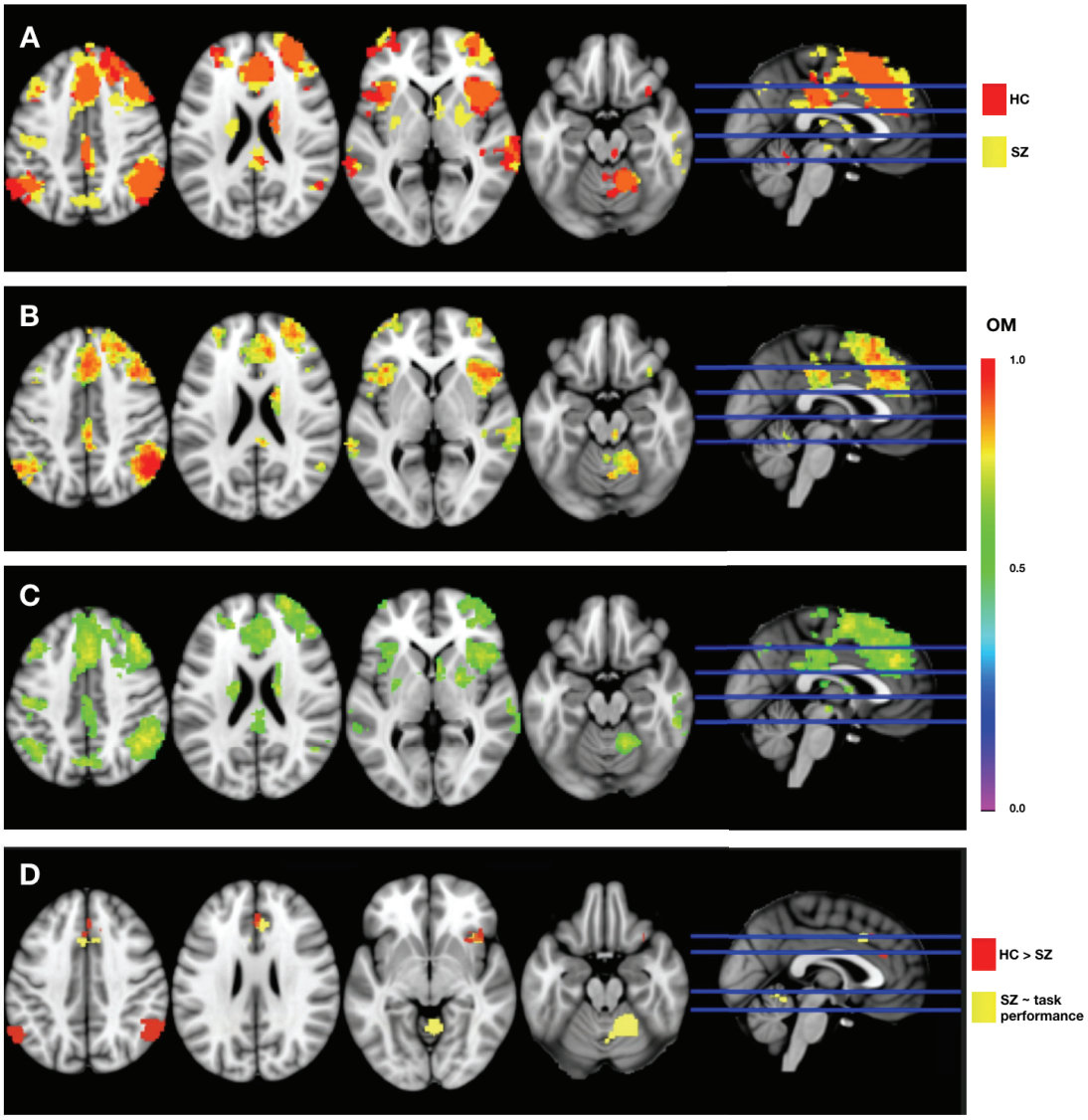

Figure 4. Mean activation findings and overlap maps. A) Significant clusters for healthy controls (red) and schizophrenia patients (yellow) in the contrast voluntary switching > automatic switching. Overlap maps (OM) for controls (B) and patients (C), masked for significant within-group clusters. D) Significant clusters of reduced activation in patients in comparison with controls (red) and positive correlation between behavioral performance

and mean activation in patients' group (yellow). Left hemisphere is shown in the left side. HC, healthy controls; SZ, schizophrenia patients.

Voxel-wise correlation analyses (Figure 4D, yellow) showed an association between task performance and activation in patients in right cerebellum (z_{max} = 6.06, 836 voxels), left pre-postcentral (z_{max} = 4.72, 570 voxels), anterior cingulate (z_{max} = 4.28, 249 voxels) and right anterior insula (z_{max} = 3.97, 100 voxels). The higher the activation, the better the task performance. No significant association with task performance was found in healthy controls. Correlation analyses in patients group showed no significant association between activation and clinical symptoms severity, including PANSS factors and CAINS total score and subscales.

Interindividual variability

Overlap maps

The pattern of activation was more consistent across subjects in healthy controls than in patients. The average value of the overlap map within the significant clusters of within-group mean activation was higher in controls (mean = 0.79, range = [0 1]) than patients (mean = 0.67, range = [0 0.86]). All within-group clusters showed similar results in parietal (left: OM_{HC} = 0.83, OM_{SZ} = 0.68; right: OM_{HC} = 0.86, OM_{SZ} = 0.7), anterior insula (left: OM_{HC} = 0.81, OM_{SZ} = 0.66; right: OM_{HC} = 0.83, OM_{SZ} = 0.67), superior and middle frontal gyrus (left: OM_{HC} = 0.77, OM_{SZ} = 0.68; right: OM_{HC} = 0.83, OM_{SZ} =0.7), pre-postcentral (left: OM_{HC} = 0.81, OM_{SZ} = 0.7; right: OM_{HC} = 0.81, OM_{SZ} =0.68) and dorsal anterior cingulate cortex (OM_{HC} = 0.83, OM_{SZ} = 0.69). When we recomputed overlap maps with lower z_{max}, we found no changes in OM values in patients' group in any cluster (see Table S3 in Supplementary Material), suggesting that lower OM values in patients did not arise from the existence of subgroups, but rather from a reduction of activation consistent across subjects.

Deviation Maps

All voxels with significant within-group mean activation (figure 4A) also showed a significant intersubject variability (deviation) in both groups, with local maxima in right anterior insula, bilateral angular gyrus, left pre-postcentral gyri and right middle frontal gyrus (see Table S4 in Supplementary Material for detailed information).

Voxel-wise correlation analyses showed a significant negative association between intersubject variability (deviation) and task performance in right cerebellum (t_{max} = -6.87, 742 voxels, MNI coordinates = 16, -52, -20), left postcentral gyrus (t_{max} = -5.46, 641 voxels, MNI coordinates = -42, -22, 60), right anterior insula (t_{max} = -4.7, 249 voxels, MNI coordinates =38, 20, -6) and paracingulate cortex (t_{max} = -4.14, 327 voxels, MNI coordinates = 8, 32, 30). The higher the departure from within-group mean activation, the lower the task performance. These clusters overlap with the map of correlation between task performance and mean activation (Figure 5A). No significant association was found between intersubject variability (deviation) and task performance in healthy controls.

Voxel-wise group comparison showed increased deviation in patients in superior frontal gyrus (t_{max} = 3.97, 87 voxels, MNI coordinates = -4, 36, 50) and left supplementary motor area (t_{max} = 3.94, 94 voxels, MNI coordinates = -10, -6, 50) (Figures 5B). No clusters of decreased deviation were found in patients. We restricted voxel-wise analysis of deviation to those voxels with significant mean activation. However, significant results were not driven by the number of voxels analyzed, since voxel-wise whole-brain analyses showed the same significant clusters in both group comparison and correlation analyses, and no additional clusters were found outside the mask.

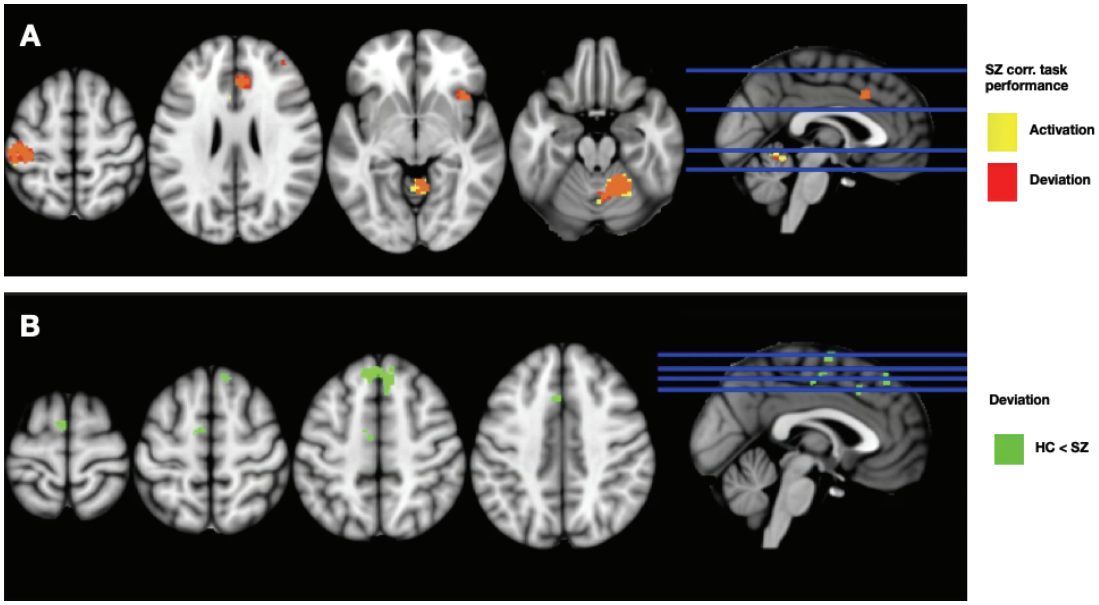

Figure 5. Intersubject deviation findings. A) Clusters with significant positive correlation between task performance and mean activation (red) and intersubject deviation (yellow) in patients' group. B) Clusters with increased intersubject variability in patients in comparison with healthy controls. HC, healthy controls; SZ, schizophrenia patients.

ROI analysis

Hypoactivated regions in patients also showed abnormalities in intersubject variability (deviation). Patients showed reduced deviation in right anterior insula (W=2167, p<0.00001) and left angular (W=2387, p_{cor}<0.00001), but increased deviation in dorsal anterior cingulate (W=845, p_{cor}=0.015), and no differences in right angular cluster.

Regions with increased intersubject variability (deviation) in patients were negatively correlated with task performance in both clusters (supplementary motor area: r=-0.30, p_{cor}=0.017; superior frontal: r=0.31, p_{cor}=0.016), but no group differences were found in mean activation, even at uncorrected level. When patients' group was subdivided in three subgroups depending on the degree of deviation, we found evidence of divergent patterns of activation (Figure 6C-D). In comparison with healthy controls, high deviation subgroup of patients showed

hypoactivation (supplementary motor area: W=658, p_{cor}=0.02; superior frontal: W=738, p_{cor}<0.00001), while low deviation subgroup exhibited hyperactivation (supplementary motor area: W=187, p_{cor}<0.00001; superior frontal: W=186, p_{cor}<0.00001). The middle deviation subgroup did not differ from healthy controls, even at uncorrected level.

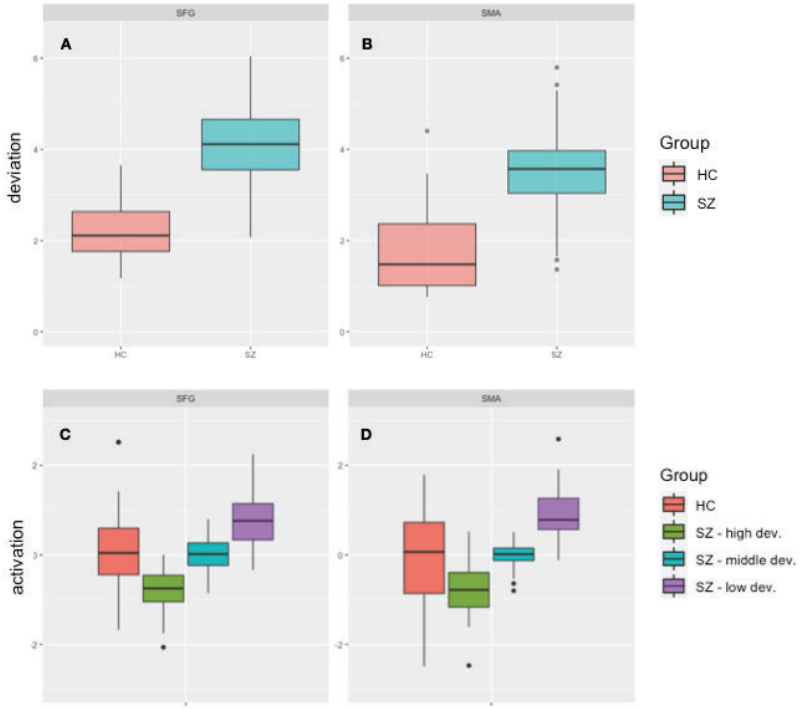

Figure 6. ROI analysis on clusters of increased interindividual variability (deviation) in patients in A) superior frontal gyrus (SFG), and B) supplementary motor area (SMA). Deviation in y-axis refers to subject-specific within-group deviation, in units of standard deviation. Note that deviation is computed as individual z-value minus group z-value. Bottom row shows activation in healthy controls (HC) and subgroups of patients with schizophrenia (SZ) with high, middle and low deviation in C) superior frontal gyrus (SFG) and D) supplementary motor area (SMA). Activation (y-axis) refers to average within-cluster cope values after regressing out age, sex, premorbid IQ, current IQ and head motion.

Then, we assessed clinical symptoms severity between subgroups of patients derived from the pattern of deviation (Tables S5 and S6 in Supplementary Material). Figure 7 shows pairwise subgroup comparison of negative symptoms severity. In supplementary motor area, high deviation subgroup showed greater negative factor, in comparison with both middle deviation (W= 625.50, p_{cor}=0.03), and low deviation subgroups (W= 638.50, p_{cor}=0.04). In superior frontal gyrus, high deviation subgroup showed greater scores, in comparison with low deviation subgroups, in negative factor (W=653.5, p_{cor}=0.023), CAINS total (W=686.5, p_{cor}=0.009), and CAINS Map (W=713, p_{cor}<0.00001). Moreover, middle deviation subgroup also showed greater CAINS Map scores than low deviation subgroup (W=273, p_{cor}=0.04). In summary, patients with hypoactivation (high deviation subgroup) in SMA and SFG showed more severe negative symptoms than patients with hyperactivation (low deviation subgroup). Moreover, in SFG, the association between hypo/hyperactivation and negative symptoms depends on the severity of the domain of apathy-avolition, but not expressivity deficits. On the contrary, we found no evidence of significant association between negative symptoms scores and mean activation in SMA and SFG clusters when correlation analyses were performed in the whole-group of patients (Figure 8).

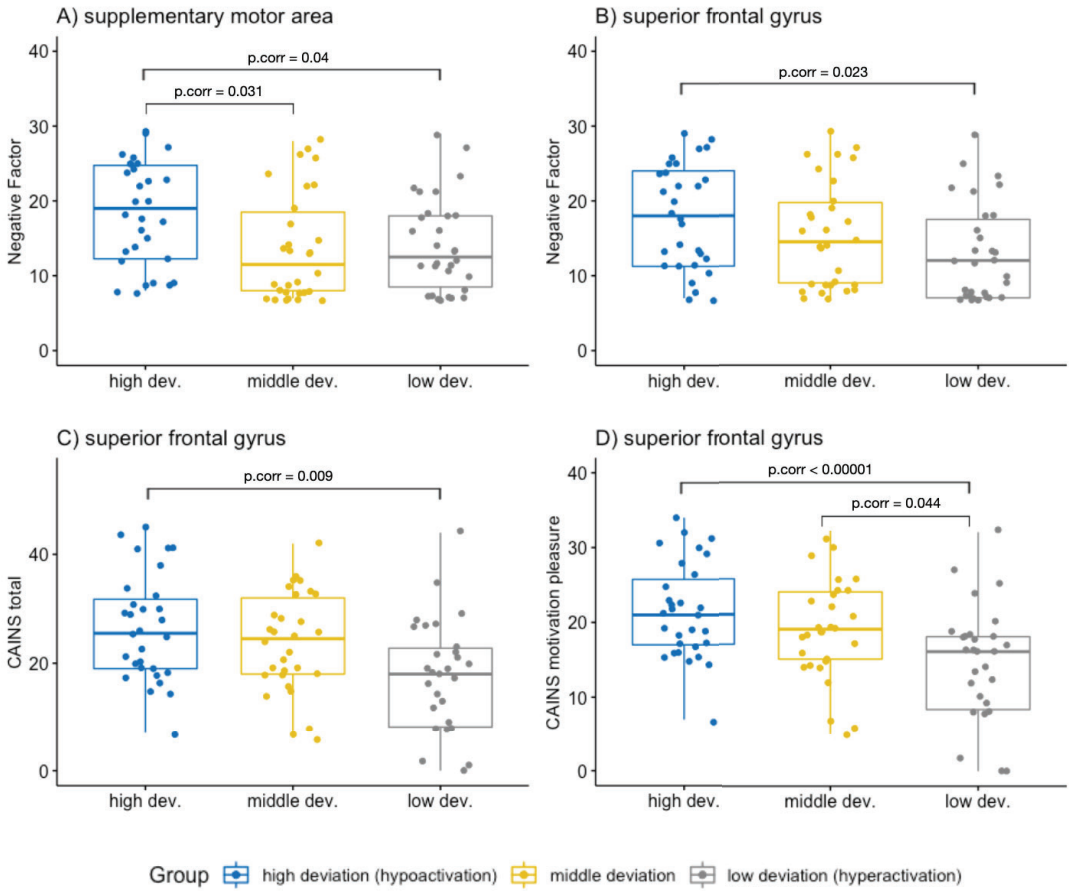

Figure 7. Group comparison of negative symptoms scores between subgroups derived from clusters of higher deviation in patients in supplementary motor area (A) and superior frontal gyrus (B-D). Note that 'high deviation' subgroup showed hypoactivation, 'low deviation' subgroup showed hyperactivation, and 'middle deviation' subgroup showed no activation difference with controls. Pairwise comparisons in negative factor (A-B), CAINS total (C) and CAINS subscale of motivation and pleasure (D), were performed with Wilcoxon test, after controlling for age, sex, premorbid IQ, current IQ, and head motion. *p.corr*, corrected p-value.

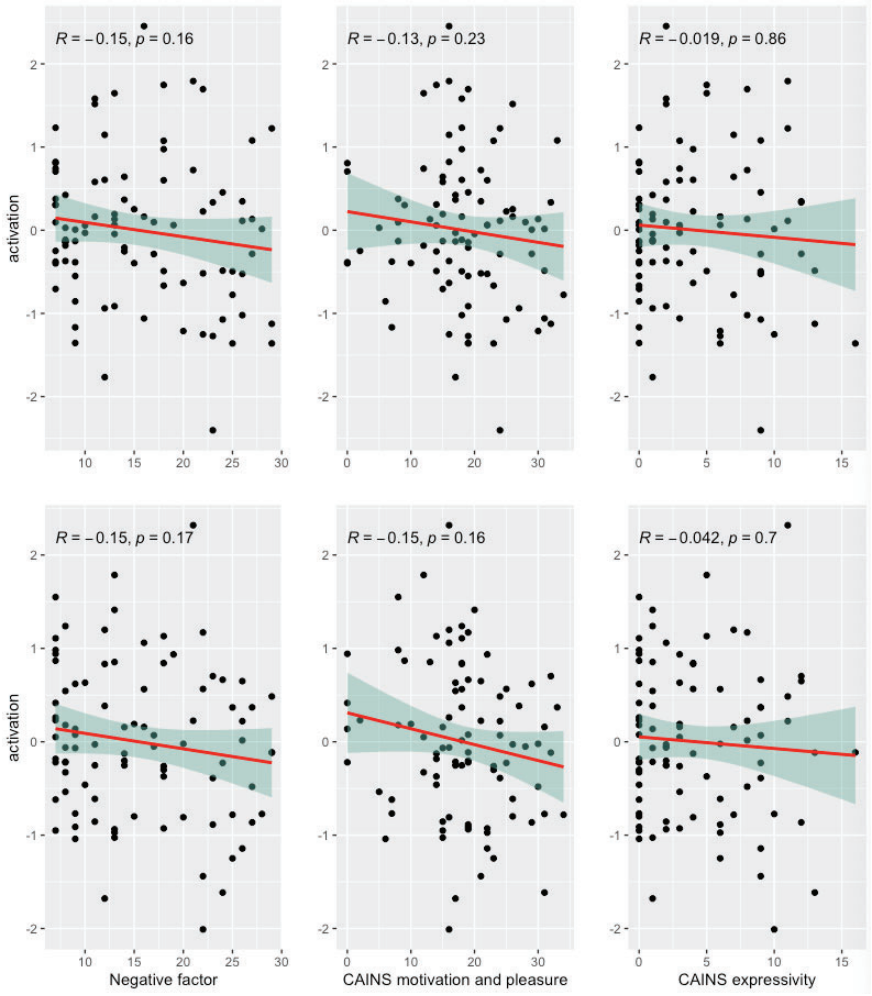

Figure 8. Correlation between negative symptoms scores and activation in supplementary motor area (top row), and superior frontal gyrus (bottom row). R, spearman correlation; p, uncorrected p-value. Activation (y-axis) refers to average within-cluster cope values after regressing out age, sex, premorbid IQ, current IQ and head motion.

DISCUSSION

The main findings of the current study are 1) patients and controls showed overlapping patterns of activation associated with goal management, 2) patients showed hypoactivations in core regions of frontoparietal and cingulo-opercular networks, and 3) the activation in those regions positively correlated with task performance. Beyond activation abnormalities, we also reported alterations in intersubject variability: 1) hypoactivated regions also showed abnormalities in interindividual variability, and 2) additional prefrontal regions showed increased intersubject variability in patients, which arose from divergent patterns of hypo- / hyper-activation depending on the severity of apathy-avolition symptoms.

At behavioral level, we found no association between clinical symptoms scores and task performance. It was an unexpected result, particularly for the negative symptoms. Correlation with CAINS MAP subscale showed a trend to significance (Figure 2), but it disappeared when covariates of no-interest were included (Figure 3). Previous studies reported significant correlations with weak-to-moderate effect sizes between negative symptoms severity and executive dysfunction measured with in-lab cognitive tasks (60,158), the Wisconsin Sorting Card Test (159,211) and the BADS battery (160). However, studies that assessed executive functions in a more ecological way, i.e., multitasking capabilities through the Computerized Meeting Preparation Task (CMPT), reported no significant correlation between different aspects of task performance and negative symptoms (212,213).

In the fMRI validation of CMET task (193), the pattern of mean activation associated with executive functions comprised regions from both frontoparietal (executive) and cingulo-opercular (salience) networks, in agreement with the notion that high-cognitive functions arises from the dynamic interaction of distributed brain areas (214,215). In the current study, the pattern of activation in patients with schizophrenia was highly overlapping with the one observed in controls, although patients showed a significant reduction in the activation of core regions of salience network (i.e., right anterior insula / frontal operculum and paracingulate / dorsal anterior cingulate), and posterior regions of frontoparietal network (i.e., bilateral angular gyri), in addition to right cerebellum and left pre-postcentral cortex. Crucially, regions with hypoactivation in patients were positively correlated with task

performance, even after correcting by age, sex, premorbid IQ, current IQ, antipsychotic medication and head motion. Besides left pre-postcentral, which might be related to the right-hand motor response required for switching games in the voluntary condition, the remaining hypoactivated regions reflected brain abnormalities associated with goal neglect.

Our findings partially agrees with Minzenberg and colleagues (19), who meta-analyzed 41 fMRI studies of executive functions in schizophrenia, and reported overlapping activation patterns in patients and controls, but hypoactivation in left dorsolateral prefrontal and rostral-dorsal anterior cingulate, among other regions. Our results also agrees with fMRI studies with the Wisconsin sorting card test reporting functional abnormalities in dorsal anterior cingulate (216,217). However, we found no hypoactivation in dorsolateral prefrontal, although bilateral superior frontal gyrus showed an hypoactivation in patients with apathy-avolition symptoms (see below). The overall pattern of results resonates with the control-conflict loop theory (110,218–220), that posits a dynamic processing loop between anterior cingulate cortex (ACC) / pre-supplementary motor area (pre-SMA), and dorsolateral prefrontal cortex (DLPFC). ACC/pre-SMA mediates task monitoring, identifying brain states suggestive of the necessity of cognitive control, while DLPFC exerts a direct control over the task-relevant circuits in order to make them support the ongoing goal-directed behavior. In the current study, both lateral and medial prefrontal regions were activated in controls and patients, but only medial regions showed reduced activation in all patients, i.e., dorsal anterior cingulate, which might reflect the sensibility of CMET task to capture brain abnormalities associated with the cognitive control subdomain of performance monitoring.

Within cingulo-opercular (salience) network, we also observed abnormalities in right anterior insula, which has been identified as a region involved in response inhibition (221), error processing (222), interference resolution (223) and, more broadly, in the maintenance of stable task-set representations (224) or general domain attentional control (225). In patients with schizophrenia, anterior insula has been consistently identified as a core region of convergence of structural (226,227) and functional abnormalities (15,16), and has been considered crucial in the development of large-scale abnormalities in the connectivity between task-positive frontoparietal (central executive) and task-negative default mode networks, the triple network dysfunction theory of schizophrenia (228–230). Beyond salience

network, we also observed hypoactivations in the posterior cores of frontoparietal (central executive), in agreement with Minzenberg and colleagues (19), who reported hypoactivations in an overlapping region in the right hemisphere. Parietal hypoactivations might also reflect connectivity deficits within frontoparietal network previously identified during the execution of working memory tasks (231) and at rest (15,16).

Variability analysis

Overlap maps and voxel-wise analysis on interindividual variability (deviation maps) suggested that brain abnormalities associated with executive dysfunction were not driven by intersubject variability across patients. This result contrasts with resting-state fMRI studies that reported increased interindividual variability in widespread brain networks (189–191,194), which might suggest that increased variability in patients appears more clearly with multivariate analysis of functional connectivity than with univariate analysis of fMRI task-evoked responses, probably because the former approach is well suited to capture variability in dysconnectivity patterns (17,18).

ROI analysis showed that hypoactivated regions in patients did differ in intersubject variability. In comparison with controls, patients showed reduced variability in right anterior insula and left angular clusters, core regions of central executive and salience networks, which may suggest a shared underlying mechanism across the disorder (48,49). Future studies with medication-naive first-episode patients should disentangle whether common abnormalities that we observed in chronic patients reflect a common etiopathology or just the common end station of etiologically divergent anomalies. Interestingly, dorsal anterior cingulate showed increased variability across patients, which might reflect that the hypoactivation observed in this region arose from heterogeneous neurobiological alterations across patients. Previous studies of structural MRI suggested the opposite, i.e., decreased variability in dorsal anterior cingulate volume across patients (49), although posterior studies did not replicate it (188), and the correspondence between structural and functional brain variability still remains to be solved (232).

As described above, we found no activation abnormalities in dorsolateral prefrontal in the whole-sample, in contrast with Minzenberg and colleagues (19), but we did find abnormalities in intersubject variability in superior frontal and

left supplementary motor area that negatively correlated with task performance. ROI analysis on deviation subgroups revealed that, in both regions, patients with larger departures from within-group mean activation showed hypoactivations, while patients with smaller departures showed hyperactivations, in comparison with controls, after controlling for age, sex, premorbid IQ, current IQ and motion. Crucially, patients with hypoactivation showed significantly more severe negative symptoms than patients with hyperactivation, particularly apathy-avolition symptoms in superior frontal gyrus.

Previous studies reported an association between apathy and deficits in goal-directed activity in schizophrenia (129,166,233), but also see (91). Despite the frontal hypothesis of negative symptoms is not new (154–156), no consistent imaging evidence reported, to our knowledge, prefrontal functional abnormalities associated with goal neglect and apathy-avolition in schizophrenia (72,169). Several factors might explain the lack of previous results. Most studies used neuropsychological tests and cognitive tasks to assess executive functions (19,171), with poor ecological validity that fail to generalize to daily-life situations (172,173). On the contrary, our task was designed to assess goal management in an ecological way, mimicking the daily life demands of cognitive control. Another factor might be the conceptualization of negative symptoms, that evolved from a unidimensional construct (234) into a multidimensional construct with two domains of symptoms, apathy/avolition vs expressivity deficits (74,235), or even five independent constructs (103,104,169). Our results encourage future studies to use ecological tasks to measure executive dysfunction and to assess negative symptoms with novel tools that accounts for its bi- or multidimensional structure.

Nevertheless, we found no association between clinical symptoms and brain activation in voxel-wise correlation analyses. Among other factors (statistical power or multiple comparisons correction of whole-brain analyses), our results might also suggest a non-linear relationship between negative symptoms and brain activation in superior frontal cortex, hindering the ability to detect them with correlation analyses (see subgroup analysis in Figure 7, and whole-group correlation in Figure 8). Future studies might confirm whether such abnormality reflects a gradient or qualitatively different subgroups of patients (58,107). These results highlight the usefulness of studying intersubject

variability in schizophrenia (199,236), which led us to the discovery of subgroups of patients with divergent patterns of hypo- and hyperactivation in superior frontal gyrus depending on the severity of apathy-avolition symptoms.

Conclusion

In summary, goal management deficits in schizophrenia were associated with a pattern of hypoactivation in core regions of cingulo-opercular (salience) and posterior regions of the frontoparietal (central executive) networks. Goal management deficits were also associated with abnormalities in intersubject variability in patients. Variability analysis also revealed that brain activation in superior frontal gyrus was modulated by the severity of apathy-avolition symptoms, but not expressivity deficits, supporting the hypothesis of executive dysfunction of the motivational domain of negative symptoms.

SUPPLEMENTARY MATERIAL

Table S1. Regions of activation in the patient and control groups in the contrast voluntary vs automatic switching.

Region	MNI coordinates			Z–score	Cluster size	*p*-value
	x	*y*	*z*			
Healthy controls						
Paracingulate cortex	2	18	48	6.25	9730	<0.001
Superior Frontal (midline)	2	28	38	5.95		
Middle Frontal (right)	42	20	42	5.9		
Anterior Insula (right)	36	18	-10	5.88		
Frontal Pole (right)	32	48	26	5.85		
Angular gyrus (right)	50	-58	40	6.43	1968	<0.001
Precentral gyrus (left)	-38	-18	62	5.22	1368	<0.001
Angular gyrus (left)	-46	-56	50	5.12	1281	<0.001
Cerebellum	12	-58	-14	4.71	798	<0.001
Posterior cingulate	2	-24	38	4.58	796	<0.001
Frontal operculum (left)	-38	22	2	5.17	777	<0.001
Frontal pole (left)	-30	54	8	4.6	763	<0.001
Schizophrenia patients						
Paracingulate cortex	6	34	32	7.3	12838	<0.001
Middle Frontal (right)	42	16	44	6.77		
Superior Frontal (midline)	6	24	50	6.48		
Anterior insula (right)	40	20	0	6.26	3254	<0.001
Angular gyrus (right)	46	-56	36	6.74	2176	<0.001
Postcentral (left)	-44	-20	46	5.71	1723	<0.001
Cerebellum	14	-52	-24	5.76	882	<0.001
Superior Temporal (right)	64	-18	-2	4.69	685	<0.001
Lateral occipital (right)	-40	-64	36	4.96	595	<0.001
Middle Temporal (left)	-50	-32	-8	4.56	481	<0.001

Table S2. Regions of deactivation in the patient and control groups in the contrast voluntary vs automatic switching.

Region	MNI coordinates			Z–score	Cluster size	*p*-value
	x	*y*	*z*			
Healthy controls						
Medial prefrontal	-2	56	-14	4.29	272	<0.001
Schizophrenia patients						
Medial prefrontal	0	54	-16	7.3	454	<0.001
Inferior temporal (left)	-40	-56	-6	6.77	139	<0.001
Lateral occipital (left)	-40	-82	24	6.48	101	<0.001

Table S3. Overlap maps at different z_{max} thresholds.

Mask - cluster	**z_{max} = 3.1**	**z_{max} = 2.7**	**z_{max} = 2.3**	**z_{max} = 2**
Within-group mean activation in SZ	0.68	0.67	0.66	0.65
Anterior insula (right)	0.64	0.64	0.63	0.62
Paracingulate cortex	0.72	0.72	0.71	0.69
Angular gyrus (left)	0.43	0.43	0.42	0.41
Angular gyrus (right)	0.67	0.66	0.65	0.64

Average values of overlap maps in patients computed with different upper thresholds (z_{max}) across the active voxels in the contrast voluntary vs automatic switching (first row), and significant clusters of reduced activation in patients (rows 2 to 5).

Table S4. Local maxima of within-group intersubject variability.

Region	**MNI coordinates**			**Z–score**
	x	***y***	***z***	
Healthy controls				
Postcentral (left)	-50	-35	61	25.1
Anterior insula (right)	32	24	-2	24.9
Angular gyrus (right)	46	-60	40	24.8
Middle frontal gyrus (right)	34	14	54	23.7
Frontal pole (right)	22	50	26	22.4
Angular gyrus (left)	-52	-54	50	22.1
Anterior insula (left)	-36	8	8	20.4
Schizophrenia patients				
Paracingulate gyrus	8	34	32	55.3
Middle frontal gyrus (right)	38	30	40	54.5
Angular gyrus (right)	58	-54	44	52
Anterior insula (right)	42	22	2	47.7
Posterior cingulate gyrus	14	-50	30	46.6
Precentral (left)	-32	-16	64	45.8

Table S5. Demographic and clinical data from subgroups of patients delineated from the pattern of intersubject variability in supplementary motor area.

	high deviation	middle deviation	low deviation
Age	43.68 ± 11.99	42.38 ± 9.54	41.23 ± 10.93
Sex (F/M)	10/21	16/13	11/21
Premorbid IQ	98 ± 8.34	97.61 ± 8.89	100.75 ± 7.37
Current IQ	95.39 ± 13.18	90.22 ± 13.51	94.7 ± 11.75
Head motion	0.06 ± 0.02	0.06 ± 0.02	0.06 ± 0.02
Negative factor	18.32 ± 6.87	13.76 ± 7.27	14.07 ± 6.3
Positive factor	7.81 ± 3.22	7.31 ± 3.17	7.4 ± 3.36
Affective factor	12.97 ± 5.38	12.76 ± 4.61	12.97 ± 4.6
Cognitive factor	18.87 ± 4.41	18.76 ± 5.53	18.1 ± 4.94
CAINS total	24.77 ± 10.53	21 ± 11.5	21.3 ± 9.95
CAINS Map	19.45 ± 7.78	17.93 ± 8.59	17.13 ± 7.37
CAINS Exp	5.32 ± 4.42	3.07 ± 4.19	4.17 ± 3.62

Table S6. Demographic and clinical data from subgroups of patients delineated from the pattern of intersubject variability in left superior frontal gyrus.

	high deviation	middle deviation	low deviation
Age	45.42 ± 9.94	44.69 ± 11.25	37.2 ± 9.59
Sex (F/M)	14/17	20/9	11/19
Premorbid IQ	98.31 ± 7.57	98.31 ± 8.43	99.76 ± 8.92
Current IQ	91.5 ± 12.77	92.48 ± 14.13	96.53 ± 11.56
Head motion	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02
Negative factor	17.74 ± 6.97	15.48 ± 7.14	13 ± 6.48
Positive factor	7.19 ± 2.68	7.79 ± 3.38	7.57 ± 3.64
Affective factor	12.55 ± 4.45	12.59 ± 5.62	13.57 ± 4.47
Cognitive factor	19.42 ± 5.12	18.93 ± 5.18	17.37 ± 4.36
CAINS total	26.52 ± 9.69	23.69 ± 9.31	16.9 ± 10.9
CAINS Map	21.61 ± 6.38	19.07 ± 7.06	13.8 ± 8.23
CAINS Exp	4.9 ± 4.28	4.62 ± 4.27	3.1 ± 3.79

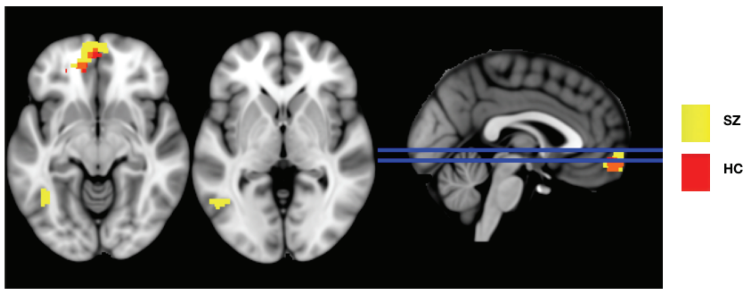

Figure S1. Significant clusters of deactivations in the contrast voluntary vs automatic switching in patients with schizophrenia (SZ, yellow) and healthy controls (HC, red).

Interindividual variability of functional connectome in schizophrenia

Goal 3. Study of interindividual variability of functional connectome in schizophrenia, by means of resting-state fMRI data, and its association with the topological properties of resting-state networks and clinical symptoms severity.

Santo-Angles A, Salvador R, Gomar JJ, Guerrero-Pedraza A, Ramiro N, Tristany J, et al. Interindividual variability of functional connectome in schizophrenia. Schizophr Res. 2021;235(January):65–73. doi: 10.1016/j.schres.2021.07.010.

Schizophrenia Research 235 (2021) 65–73

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Interindividual variability of functional connectome in schizophrenia

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ARTICLE INFO

Keywords:
Resting-state fMRI
Functional connectome
Interindividual variability
Brain heterogeneity
Graph theory
Schizophrenia
Negative symptoms

ABSTRACT

Schizophrenia is a complex psychiatric disorder that displays an outstanding interindividual variability in clinical manifestation and neurobiological substrates. A better characterization and quantification of this heterogeneity could guide the search for both common abnormalities (linked to lower intersubject variability) and the presence of biological subtypes (leading to a greater heterogeneity across subjects). In the current study, we address interindividual variability in functional connectome by means of resting-state fMRI in a large sample of patients with schizophrenia and healthy controls. Among the different metrics of distance/dissimilarity used to assess variability, geodesic distance showed robust results to head motion. The main findings of the current study point to (i) a higher between subject heterogeneity in the functional connectome of patients, (ii) variable levels of heterogeneity throughout the cortex, with greater variability in frontoparietal and default mode networks, and lower variability in the salience network, and (iii) an association of whole-brain variability with levels of clinical symptom severity and with topological properties of brain networks, suggesting that the average functional connectome overrepresents those patients with lower functional integration and with more severe clinical symptoms. Moreover, after performing a graph theoretical analysis of brain networks, we found that patients with more severe clinical symptoms had decreased connectivity at both whole-brain level and within the salience network, and that patients with higher negative symptoms had large-scale functional integration deficits.

1. Introduction

Schizophrenia is a complex psychiatric disorder that displays a remarkable interindividual variability in terms of clinical symptoms (Tsuang et al., 1990), cognitive impairment (Van Rheenen et al., 2017), treatment response (Malhotra, 2015) and prognosis (Huber, 1997). The neurobiological and genetic substrate of the disorder also shows a prominent heterogeneity (Buchsbaum, 1979; Kahn et al., 2015).

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https://doi.org/10.1016/j.schres.2021.07.010
Received 13 January 2021; Received in revised form 8 July 2021; Accepted 11 July 2021
Available online 27 July 2021

However, most studies have, so far, treated this variability as noise, focusing on the search for mean group differences between patients and controls. While this approaches identified genetic and environmental factors associated with schizophrenia (Owen et al., 2016; Radua et al., 2018)and its common structural and functional brain abnormalities (Dong et al., 2018; Minzenberg et al., 2009; van Erp et al., 2018), reliable neuroimaging-based biomarkers of diagnosis, prognosis or treatment remain to be developed. For this reason, there is an emerging interest in the identification of biologically homogeneous subtypes of patients (Insel et al., 2010; Kapur et al., 2012) which, in turn, may be facilitated by a proper characterization and quantification of interindividual variability. The heterogeneity in biological processes underlying the disorder and the related inclusion of patients with different biological subtypes under the same diagnostic category will probably be associated with higher interindividual variability in certain brain circuits or mechanisms, while lower variability may be due to common abnormalities shared across the disorder (Brugger et al., 2020; Brugger and Howes, 2017).

The functional connectome is an excellent target for studying interindividual variability of brain function (Dubois and Adolphs, 2016; Seghier and Price, 2018). It is defined as the individual profile of functional connectivity, i.e. the statistical dependence of neuronal activity between brain regions computed from fMRI data (Eickhoff and Müller, 2015; Sporns, 2010). The functional connectome is unique for each subject and stable over time (Finn et al., 2015; Horien et al., 2019). Interestingly, intersubject variability of the functional connectome is not homogeneously distributed throughout cerebral cortex, with largest heterogeneities reported for high-order association areas (Mueller et al., 2013). Moreover, variability in the spatial distribution of resting-state networks has been shown to be stable over time, related to functional task-evoked variations and having behavioural correlates (Gordon et al., 2017; Seitzman et al., 2019).

Variability in functional connectivity has been previously studied in schizophrenia. Thus, Gopal et al. (2016) reported higher spatial variance in resting-state networks in schizophrenia, particularly in the basal ganglia and the bilateral temporal, sensorimotor and visual networks. Chen et al. (2018) also reported greater heterogeneity in the spatial distribution of resting-state networks, mainly in primary sensory areas, and higher variability in whole-brain functional connectome in patients than in healthy controls. These authors also showed that deviations from a common-cohort pattern of functional connectivity were associated with lower global efficiency and with increased genetic vulnerability to schizophrenia.

In the current study we address interindividual variability in functional connectome by means of resting-state functional MRI in a sample of patients with schizophrenia and healthy controls matched by age, sex and premorbid IQ. We extend previous studies in several ways. First, we quantify the dissimilarity between functional connectomes at the individual and group levels using, among other metrics, the geodesic distance. This metric computes the distance between functional connectivity matrices considering its non-Euclidean geometry, and it has been recently shown to outperform Pearson's dissimilarity for subject identification using functional connectivity data (Venkatesh et al., 2020). Second, in addition to studying variability at the whole-brain level we have also analysed within-network variability in functional connectivity. Third, to address the interpretation of variability in functional connectome, we have explored its association with the severity of clinical symptoms and with the topological properties of brain networks.

2. Methods

2.1. Participants

For our study we have reanalysed a subset of the sample used by Salvador et al. (2017) including 110 patients with schizophrenia and 110 healthy subjects matched by age, gender and pre-morbid IQ as estimated with the Word Accentuation Test (Gomar et al., 2011). Table 1 provides extensive information on both samples (see Supplementary material for inclusion/exclusion criteria). Clinical symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) available in a subsample of 95 patients. Following Chen et al. (2020), we clustered PANSS items in four factors: negative, positive, affective and cognitive (individual items included in each factor are listed in the Supplementary material).

2.2. Data acquisition and preprocessing

All subjects underwent a 9 minute MRI scanning session with open eyes to avoid falling asleep. Resting state fMRI data was obtained using a gradient echo echo-planar (EPI) sequence. Images were preprocessed using FSL (Smith et al., 2004), including registration, slice timing correction, temporal filtering and spatial smoothing. Minimization of noise due to head motion, MRI susceptibility artifacts and non-brain physiological signal was performed using FIX, an automated ICA-based denoising approach (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Specifically, we trained the FIX classifier using a sample of 20 subjects: 10 patients and 10 healthy controls, matched by age, sex and premorbid IQ. Following the guidelines provided by Griffanti et al. (2017), we labeled 89.6% [range 81–98] of components in the training sample as noise, in agreement with previous reports using 1.5 T scans (Griffanti et al., 2015). Then, the components of the remaining subjects were classified as noise or signal using the classifier. The threshold that determined the binary classification of any component was set to 20, allowing a balance between true positive and true negative rates (77.5% and 81.2%, respectively, in the training sample). Finally, we regressed out noise components from individual functional images. For an extensive description of acquisition parameters and the preprocessing pipeline see the Supplementary material.

2.3. Network construction

Individual functional connectomes, also referred as netmats, were created as follows. Nodes were defined using the functional atlas local-global parcellation (Schaefer et al., 2018) which includes 100 regions of

Table 1
Demographic and clinical characteristics of patients and controls.

	Patients (n = 110)	Controls (n = 110)	Statistical test
Age (years)	38.17 (10.71)	37.3 (10.71)	t(218) = 0.6, p = 0.54
Gender (M/F)	74/36	73/37	$X^2(1) = 0.02$, p = 0.88
Premorbid IQ (TAP)[a]	100.88 (8.32)	101.75 (8.41)	t(194.94) = 0.47, p = 0.47
Current IQ (WAIS-III)[b]	92.39 (16.92)	107.17 (15.59)	t(187.94) = −6.27, p = 2e−9
Head motion (mean FD)	0.11 (0.05)	0.07 (0.033)	t(173.54) = 7.07, p = 3e−11
Duration of psychosis (years)	15.56 (11.5)	N.A.	
Chlorpromazine equiv. (mg)[c]	507.77 (392.49)	N.A.	
PANSS total[d]	69.32 (18.86)	N.A.	
Negative factor[d]	18.37 (6.75)	N.A.	
Positive factor[d]	11.09 (4.76)	N.A.	
Affective factor[d]	15.70 (5.38)	N.A.	
Cognitive factor[d]	26.83 (8.21)	N.A.	

FD, framewise displacement; PANSS, Positive and Negative Syndrome Scale; TAP, Word Accentuation Test (Test de Acentuación de Palabras); WAIS-III, Wechsler Adult Intelligence Scale III.

[a] Premorbid IQ data from 97 healthy controls and 99 schizophrenia patients.
[b] Current IQ data from 92 healthy controls and 98 schizophrenia patients.
[c] Medication data from 99 patients.
[d] Clinical data from 95 patients.

interest (ROIs) corresponding to the 7 resting-state networks identified by Yeo et al. (2011): visual, somatomotor, dorsal attention, salience – ventral attention, limbic, frontoparietal and default mode network. Connectivity strength between nodes was defined using partial correlations. To improve the estimation of partial correlations an L2 regularization was applied (rho = 0.50 in ridge regression option of FSLNets) (Shen et al., 2018). Computed correlations were Fisher-transformed and, for each group, we calculated the average functional connectome, referred from now as group template.

2.4. Distance and graph metrics

To evaluate the variability in the functional connectome, we computed a set of metrics that quantify the deviation of each individual netmats from its group average netmats. Specifically, we calculated.

a) the Euclidean distance

$$d_e = \sqrt{\sum_{d=1}^{D} \left([C_i] - \left[\overline{C}_g \right] \right)^2}$$

where D is the number of nodes, C_i is the individual netmats and $\overline{C}_g$ is the group averaged netmats,

b) the Pearson dissimilarity

$$d_p = \frac{1 - corr\left(c_i, \overline{c}_g \right)}{2}$$

where c_i and $\overline{c}_g$ are the vectors obtained by stacking the columns of C_i and $\overline{C}_g$.,

and *c) the Geodesic distance*

$$d_g = \sqrt{\sum (log(\lambda_i))^2}$$

where λ_i for i=1, …,n are the n eigenvalues ≥0 of Q and $Q = C_i^{-1/2} C_g C_i^{-1/2}$.

Each one of these metrics quantifies the distance between matrices in different ways. Euclidean distance uses the squared difference of each element of the matrices, Pearson's dissimilarity measures distance in terms of correlation between vectorized matrices, and geodesic distance measures the shortest path between matrices along the manifold, i.e. the non-linear surface that emerges in correlation matrices. We calculated these metrics using the scripts available in the study of Venkatesh et al. (2020). Pearson's dissimilarity was Fisher-transformed.

We also computed three graph metrics with weighted networks using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010): global efficiency, local efficiency and connectivity strength. A proportional (sparsity-based) threshold was applied to remove weak correlations using a data-driven range of densities that retained the small world properties of fully connected netmats. For a detailed description of graph metrics, see Supplementary material.

2.5. Statistical analysis

We tested differences between patients and healthy subjects in graph metrics (strength, global and local efficiency) and distance metrics (Pearson's dissimilarity, Euclidean and geodesic distances) by means of Quade's Non-Parametric ANCOVA (Lawson, 1983) with mean framewise displacement (Power et al., 2012) as covariate in order to control for group differences in head motion. We did not include age, sex and premorbid IQ as covariates since both groups were matched for these three variables and neither included current IQ as a covariate because cognitive decline is a core feature of the disorder.

In the subsample of 95 patients with clinical data, we computed the Spearman's rank correlation coefficient between a) graph and distance metrics, b) graph metrics and clinical symptoms, and c) distance metrics and clinical symptoms. To quantify clinical symptom severity, we used the PANSS total scores and the four, previously mentioned, factors (negative, positive, affective and cognitive).To control for confounding effects, before computing the correlations we calculated the residuals from a linear model with the variable of interest as dependent variable (clinical, graph or distance metric) and age, sex, premorbid IQ (Word Accentuation Test), current IQ (WAIS-III) and head motion as independent variables. Then we used the residuals of the linear model for the correlation analyses. In addition, we also computed the correlation between graph and distance metrics in a subsample of healthy controls with available premorbid and current IQ data (n = 90).

The main analyses described above involved 54 statistical tests (6 group comparisons and 48 correlations) that were carried out, repeatedly, at whole-brain level and for the seven resting-state networks (visual, somatomotor, salience – ventral attention, dorsal attention, frontoparietal, limbic and default mode network) (Schaefer et al., 2018). For each one of the seven resting state networks (and whole brain analysis) we performed a separate correction for multiple comparisons using the False Discovery Rate (Benjamini and Hochberg, 1995). Corrected values at $p < 0.05$ were considered as statistically significant.

In addition to all these analyses we performed the following supplementary analyses. First, we included dose of antipsychotic medication (chlorpromazine equivalents) as a covariate in the correlation analyses. Second, we performed group comparisons in a subsample of patients (n = 99) and controls (n = 97) with premorbid IQ data. Third, in order to assess the effect of age, sex, premorbid IQ, current IQ and head motion in graph and distance metrics, we fitted a set of six linear models for each group with those variables as predictors and graph and distance metrics as outcome variables. Finally, we recomputed patients' distance metrics relative to the group average of healthy controls, and performed the same statistical analyses. Note that this changed the interpretation of distance metrics in patients. Instead of being a measure of intragroup variability, it became a measure of deviation from the control group average.

3. Results

3.1. Variability in functional connectome

At the whole-brain level, patients showed significantly higher variability than healthy controls in all distance metrics, but only differences in geodesic distance were significant after correction for multiple comparisons (HC: 14.79 ± 1.15; SZ: 15.22 ± 1.26; $F_{1,218} = 13.049$; $p = 0.0029$) (Fig. 1A). At the network level, patients had higher geodesic distance in frontoparietal (HC: 4.14 ± 0.73; SZ: 4.76 ± 0.56; $F_{1,218} = 55.2$, $p < 0.00001$) (Fig. 1B) and default mode networks (HC: 6.29 ± 0.58; SZ: 6.74 ± 0.56; $F_{1,218} = 36.9$, $p < 0.00001$) (Fig. 1C). In contrast, geodesic distance was smaller for patients in the salience – ventral attention network (HC: 3.91 ± 0.69; SZ: 3.64 ± 0.66) (Fig. 1D), although this was only significant at the uncorrected level ($F_{1,218} = 4.6$, $p_{uncorrected} = 0.032$, $p = 0.11$). No differences were found for the limbic, somatomotor and dorsal attention networks. Supplementary analyses with a subsample of subjects with premorbid IQ data showed the same results.

3.2. Network graph metrics

No significant differences between groups were found for any graph metric at the whole-brain or at the network level.

3.3. Association between distance and graph metrics

At the whole-brain level (Fig. 2), connectivity strength and distance

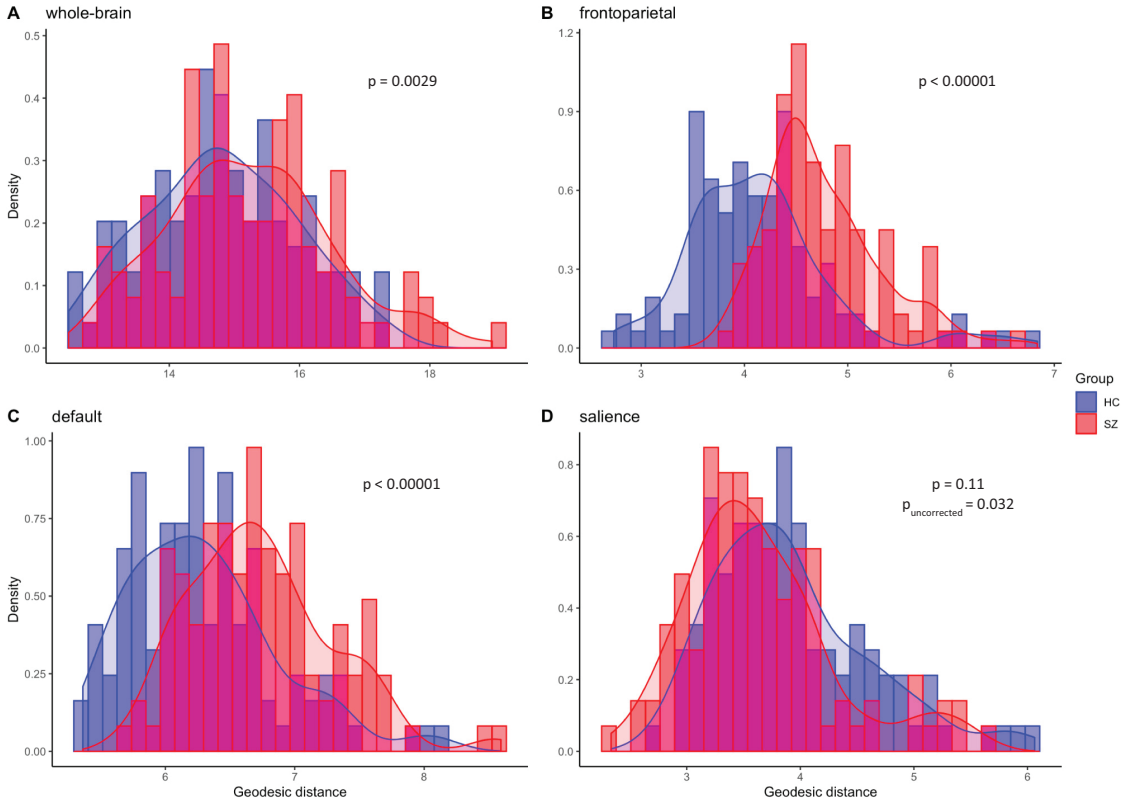

Fig. 1. Variability of functional connectome at A) whole-brain level, B) frontoparietal, C) default and D) salience – ventral attention networks. p, corrected p-value of group comparison with head motion as a covariate (Quade's Non-Parametric ANCOVA); $p_{uncorrected}$, uncorrected p-value; HC, healthy controls; SZ, patients with schizophrenia.

metrics were positively correlated in both groups: Euclidean distance (SZ: rho = 0.97, p < 0.00001; HC: rho = 0.96, p < 0.00001), Pearson's dissimilarity (SZ: rho = 0.54, p < 0.00001; HC: rho = 0.32, p = 0.012) and geodesic distance (SZ: rho = 0.95, p < 0.00001; HC: rho = 0.94, p < 0.00001). Between-network connections contributed more than within-network connections to the whole-brain correlation of connectivity strength with Euclidean and geodesic distances (see Supplementary material). Global efficiency was also positively correlated with Euclidean distance (SZ: rho = 0.34, p = 0.003; HC: rho = 0.29, p = 0.02), Pearson's dissimilarity (SZ: rho = 0.32, p = 0.003) and geodesic distance (SZ: rho = 0.36, p = 0.003; HC: rho = 0.28, p = 0.024). Local efficiency was correlated with Pearson's dissimilarity only in patients (rho = 0.24, p = 0.045). When the amount of antipsychotic medication was introduced as a nuisance factor all results remained significant.

For a detailed description of results at the network level, see the Supplementary material. Briefly, connectivity strength was positively associated with Euclidean and geodesic distances in some networks, although with weaker correlations than at whole-brain. Global efficiency was positively associated with Pearson's dissimilarity in some networks in both groups, and negatively with Euclidean distance in the frontoparietal network in patients. In contrast, local efficiency was negatively associated with distance metrics in some networks in both groups, but positively associated with Pearson's dissimilarity in the frontoparietal network in patients.

In summary, subjects with a functional connectome more deviant from their respective group template showed higher connectivity and global efficiency at whole-brain and network level, and lower within-network local efficiency.

3.4. Association between graph metrics and clinical symptom severity

At the whole-brain level (Fig. 2), connectivity strength was negatively correlated with PANSS total scores (rho = −0.26, p = 0.024) and the affective factor (rho = −0.27, p = 0.024), and the Negative factor was correlated with global efficiency (rho = −0.26, p = 0.032). At network level, only the salience – ventral attention network had significant results: connectivity strength was negatively correlated with PANSS total scores (rho = −0.30, p = 0.028) and the affective factor (rho = −0.31, p = 0.026). When antipsychotic medication was introduced as a nuisance factor, previous results remained significant.

3.5. Association between distance and clinical symptom severity

At the whole-brain level (Fig. 2), Euclidean distance was negatively correlated with PANSS total scores (rho = −0.28, p = 0.02), the affective (rho = −0.26, p = 0.32) and cognitive factors (rho = −0.24, p = 0.045), and Geodesic distance was negatively correlated with the affective factor (rho = −0.30, p = 0.016). At the network level, only the somatomotor network showed significant correlations between distance and clinical symptoms. The Geodesic distance was correlated with the negative factor (rho = −0.31, p = 0.013). When the amount of antipsychotic medication was introduced as a nuisance variable previous results remained significant.

3.6. Supplementary analyses

When the distance metrics of patients were computed relative to the

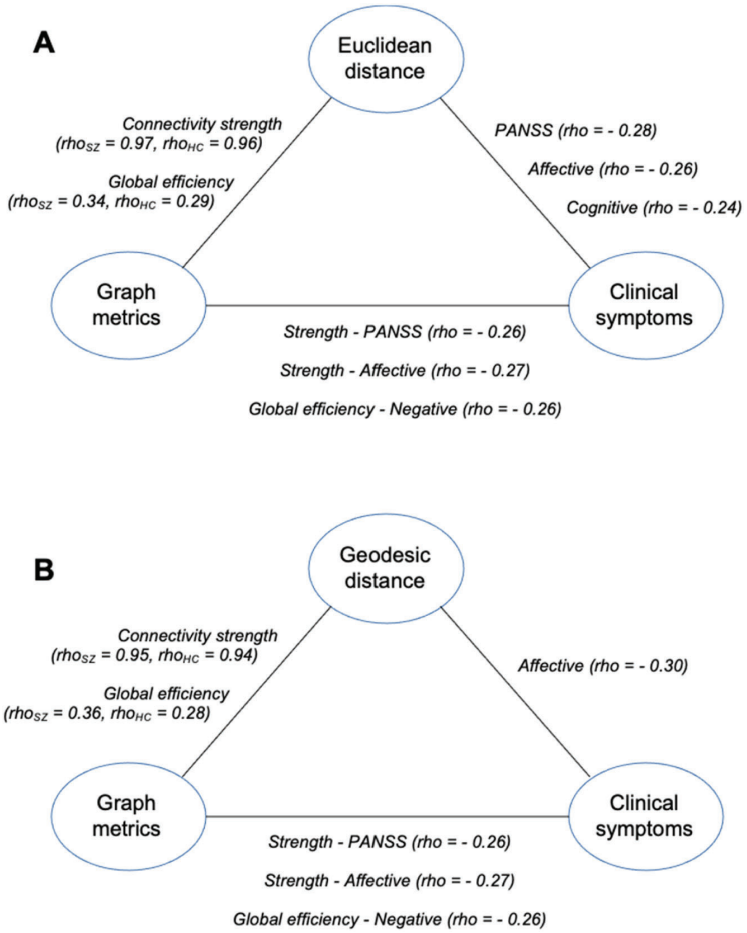

Fig. 2. Whole-brain correlations between variability in functional connectome (Euclidean distance – panel A, and geodesic distances - panel B), graph metrics (strength and global efficiency) and clinical symptom severity (PANSS total score, positive, negative, affective and cognitive factors) in patients with schizophrenia, controlling for age, sex, premorbid IQ, current IQ and head motion. rho, Spearman's full correlation coefficient.

group average of healthy controls, group differences in geodesic distance were no longer significant, but group differences in the other distance metrics emerged. At whole-brain, Euclidean distance ($F_{1,218} = 5.76$, $p = 0.043$) and Pearson's dissimilarity ($F_{1,218} = 16.33$, $p = 0.0006$) were significantly larger in patients. At within-network level, patients showed higher Euclidean distance in the default network ($F_{1,218} = 7.1$, $p_{uncorrected} = 0.008$, $p_{corrected} = 0.057$) and larger Pearson's dissimilarity values in the visual network ($F_{1,218} = 7.96$, $p_{uncorrected} = 0.0052$, $p_{corrected} = 0.063$) although these differences were significant only at the uncorrected level. In contrast, correlation analyses based on the recalculated metrics had the same significant results as those previously reported with the original metrics. Results on the effects of age, sex, premorbid IQ, current IQ and head motion on graph and distance metrics are described in the Supplementary material.

4. Discussion

In the current study, we assessed interindividual variability in functional connectome in schizophrenia by means of three distance metrics but only results with geodesic distance were robust to head motion. Moreover, geodesic distance was particularly associated with intragroup variability, which was the main subject of the study, and not deviation from healthy controls. For these reasons, the discussion is focused on those findings. The higher whole-brain variability in schizophrenia observed in our study is in agreement with previous reports (Chen et al., 2018; Gopal et al., 2016), and is consistent with the global nature of brain abnormalities in schizophrenia (Crossley et al., 2016), although abnormalities found were not equally distributed throughout the cortex.

Frontoparietal and default mode networks showed higher variability in patients, while salience network showed lower variability (at uncorrected level). These networks have been widely associated with the pathophysiology of schizophrenia: frontoparietal (Deserno et al., 2012; MacDonald et al., 2005), default (Whitfield-Gabrieli and Ford, 2012) and salience (Palaniyappan and Liddle, 2012; Sheffield et al., 2020). Recent meta-analyses reported strong evidence of functional dysconnectivity in frontoparietal, default and salience networks (Brandl et al., 2019; Dong et al., 2018), suggesting that imbalanced communication between salience and both default and frontoparietal networks may underlie the core difficulty of patients to differentiate self-representation and environmental salience processing (Dong et al., 2018). Our results extend the scope of anomalies in the intrinsic functional connectivity, providing evidence of abnormalities also in variability.

Our findings of higher variability in functional connectome at both whole-brain and network level are consistent with the substantial

evidence of heterogeneity in the neurobiological basis of schizophrenia (Buchsbaum, 1979; Kahn et al., 2015), including brain structure and function (Alnæs et al., 2019; Brugger et al., 2020; Brugger and Howes, 2017). Brugger et al. (2020; 2017) suggested that higher interindividual variability in schizophrenia could reflect heterogeneity in biological processes underlying the disorder, while lower variability could indicate the presence of common abnormalities shared across the disorder. According to this interpretation, networks where we observed higher variability (whole-brain, frontoparietal and default) could reflect divergent patterns of abnormal functional connectivity. Nevertheless, heterogeneity in functional connectome could be due to pathological processes (Brugger and Howes, 2017), compensatory mechanisms in brain connectivity (Crossley et al., 2016), or even non-pathological processes (Holmes and Patrick, 2018). On the other hand, lower variability in salience network could reflect common abnormalities in connectivity shared across the disorder. Indeed, Brugger and Howes (2017) reported one region with lower structural variability, dorsal anterior cingulate cortex, a core region of one of the networks in which we reported lower variability in functional connectome, the salience network. Despite clear differences between studies (first-episode vs chronic patients, meta-analysis vs original research, structural vs functional MRI), this is particularly interesting in light of the study of Smith et al. (2019) who recently demonstrated that structural variability throughout the entire cortex was associated with meaningful variability in the functional connectome at the population level. However, the finding of lower variability in salience network in patients should be taken with caution, since it remained significant only at uncorrected level.

To our knowledge, the current study is the first to report a correlation between clinical symptom severity and interindividual variability of the functional connectome. We observed a negative correlation between several metrics of variability in the functional connectome (geodesic and Euclidean distances) and the severity of clinical symptoms (PANSS total score, affective and cognitive factors) at the whole-brain scale, i.e., patients with a functional connectome more similar to the group template showed more severe clinical symptoms. Note that these results were robust to head motion and antipsychotic medication. It might indicate that the average functional connectome overrepresents those patients with more severe symptoms, in agreement with previous studies that have suggested the average patient is a noninformative construct (Wolfers et al., 2018).

To address the physiological interpretation of variability in functional connectome, we assessed its association with graph metrics. At the whole-brain level, all metrics of variability were positively correlated with global efficiency and connectivity strength. Higher variability was accompanied with higher functional integration of whole-brain networks in both patients and healthy controls. This result contrasts with (Chen et al., 2018), who reported a negative correlation between variability and global efficiency in patients with schizophrenia. The distinct way of defining the group template can explain this discrepancy. Chen and colleagues used a cohort-common template created with subjects from both groups of patients and controls. In the current study, the functional connectome of each subject was compared with its own group average, setting the focus on the characterization of within-group variability. Thus, current results indicate that patients with a functional connectome more similar to the group template showed less integrated brain networks. It could suggest that the average functional connectome fits well with the hypothesis of brain dysconnectivity in schizophrenia (Friston et al., 2016; Friston and Frith, 1995), although we did not find any group differences in global efficiency (see discussion on group differences in graph metrics below). Nevertheless, the association between variability and graph metrics was not specific for patients, since healthy controls showed the same pattern. It suggests that the limitations associated with group templates to study functional connectivity also extend to healthy population, biasing the template toward low levels of functional integration, probably due to the inability of the group average to capture meaningful interindividual variability in the functional connectome (Seitzman et al., 2019). Network level results, with variability positively associated with connectivity strength and global efficiency but negatively related to local efficiency, also supported this interpretation. However, in patients, the frontoparietal network, depending on the distance metric used, showed conflicting results in both global and local efficiency. Future research should carefully explore the association between variability metrics and the frontoparietal network and its subcomponents.

Connectivity strength and global efficiency showed significant associations with clinical symptoms severity. On the one hand, connectivity strength was negatively correlated with clinical symptoms at whole-brain scale and within salience network, in agreement with previous reports linking psychotic symptoms with functional coupling at whole-brain, connectivity strength of temporal and frontal regions (Skudlarski et al., 2010), and abnormal connectivity within salience and between salience and default mode network (Hare et al., 2019; Manoliu et al., 2014). On the other hand, patients with more severe negative symptoms showed lower global efficiency at whole-brain. No network showed similar results, suggesting that negative symptoms were associated with a large-scale impairment in functional integration. This result agrees with previous reports (Ma et al., 2012; Yu et al., 2011), but also see (Su et al., 2015).

The absence of group differences in global efficiency, both at whole-brain and network level, was in agreement with a meta-analysis of graph-analytical metrics in schizophrenia (Kambeitz et al., 2016). However, we did not replicate the reduction in local organization reported in this meta-analysis, since we did not find group differences in local efficiency. This discrepancy may be due to methodological issues. First, we used weighted netmats, while all the resting fMRI studies meta-analysed in Kambeitz et al. used binary netmats. Second, although we used the same method to remove false positives than most of the studies in the meta-analysis (i.e. proportional (relative) thresholding), only one study used a similar range of densities. Third, the current study has used larger sample sizes than any of the studies reported in Kambeitz et al., and while we only included chronic patients, some of the meta-analysed studies also had first-episode patients. Finally, we controlled for head motion in the group comparisons, while most of previous studies did not. Indeed, we did find a reduction in connectivity strength in patients in visual ($W = 4547.5$, $p_{uncorrected} = 0.0015$) and somatomotor networks ($W = 4441$, $p_{uncorrected} = 0.0006555$). However, those differences vanished when head motion was introduced as a nuisance factor.

Several limitations should be taken into consideration. Group differences in variability could also be related to increased motion artifacts in patients. To control for this confounding variable, we discarded all subjects who moved more than 3 mm maximum and more than 0.3 mm on average, and applied an ICA-based denoising approach that identified 75% of components of individual ICA as noise and removed them from functional images. ICA-based denoising methods have been shown to be much more successful in removing motion artifacts than nuisance regression methods, in addition to addressing other sources of noise, such as MRI susceptibility or physiological noise (Pruim et al., 2015). To increase the accuracy of the automated labelling of noise components, we decided to use ICA-FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014), in order to train the classifier with our own data, hand-labelling the components of the individual ICA of 20 subjects, as suggested by Pruim et al. (2015). In addition, we performed supplementary analyses with head motion, i.e. mean displacement framewise (Power et al., 2012), as a nuisance factor. Interestingly, only geodesic distance was robust to head motion, supporting the advantages of this metric in the study of functional connectivity (Venkatesh et al., 2020). Another possibility is that our findings could be due to factors secondary to the disorder. Indeed, some of the correlations with clinical symptoms severity lost significance when antipsychotic medication, e.g., chlorpromazine equivalence, was introduced as a covariate, although this could be due to overcorrection since patients with more severe symptoms usually have a higher dose of medication. Moreover, patients may

appear more heterogeneous if healthy controls are healthier than general population and, therefore, more homogeneous (Schwartz and Susser, 2011), although we found no group differences in variance between patients and controls in age ($F_{109,109} = 0.99$, $p = 0.99$), premorbid IQ ($F_{109,109} = 0.97$, $p = 0.91$) or current IQ ($F_{109,109} = 1.18$, $p = 0.43$).

4.1. Conclusion

The main findings of the current study are 1) the functional connectome of patients with schizophrenia is more heterogeneous across subjects, 2) variability in functional connectivity is not equally distributed throughout the cortex, but is greater in frontoparietal and default mode networks, and lower in salience network, 3) whole-brain variability was also associated with clinical symptom severity and topological properties of brain networks, suggesting that the average functional connectome overrepresents those patients with lower functional integration and more severe clinical symptoms. In addition, the graph theoretical study of brain networks showed that 4) patients with more severe affective and cognitive symptoms showed decreased connectivity at whole-brain level and within the salience network, and 5) patients with higher negative symptoms showed large-scale functional integration deficits.

Role of funding sources

All funding sources reported in 'Acknowledgements' contributed to the collection of data.

CRediT authorship contribution statement

ASA contributed to conceptualization, formal analysis and writing; JS, MB and RS reviewed and edited the manuscript; JJG, AGP, NR, JT, CT, JOG, CA, CB, LLA, TM, PSP and SS contributed to data curation; PJM and EPC contributed to project administration, supervision and resources.

Declaration of competing interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda. The other authors declare no conflicts of interest.

Acknowledgements

This work was supported by CIBERSAM and the Catalonian Government (2014-SGR-1573, 2017-SGR-1271 from AGAUR and by the Instituto de Salud Carlos III (), co-funded by European Union (ERDF/ESF, "Investing in your future"): Miguel Servet Research contracts (CPII13/00018 to RS and MS10/00596 to EP-C), and Research Projects (PI10/01058, PI14/01148, PI14/01151 and PI18/0087).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.07.010.

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SUPPLEMENTARY MATERIAL

1. METHODS

1.1. Participants

Patients were recruited from the Benito Menni CASM hospital, Sant Rafael Hospital, Sagrat Cor Hospital and Mare de Déu de la Mercé (Spain) following the DSM-IV diagnosis criteria for schizophrenia (i.e. excluding patients with schizoaffective and other schizophrenia related disorders). All individuals were right-handed, in the age range 18 to 65, with no history of brain trauma or neurological disease, and not having shown alcohol/substance abuse in the last 12 months. Healthy controls were recruited from non-medical hospital staff, their relatives and acquaintances, plus independent sources in the community. Apart from previous exclusion criteria, healthy subjects reporting a history of mental illness and/or treatment with psychotropic medication or with a psychotic first-degree relative were discarded.

Based on Chen and colleagues(Chen et al., 2020), we clustered PANSS items in the following factors: Negative factor (blunted affect, emotional withdrawal, poor rapport, apathetic social withdrawal, low spontaneity / flow, mannerisms and posturing, motor retardation), positive factor (delusions, hallucinations, grandiosity, unusual thought content), affective factor (suspiciousness / persecution, somatic concern, anxiety, guilt feelings, tension, depression, active social avoidance) and cognitive factor (conceptual disorganization, hyperactivity / excitement, hostility, difficulty in abstract thinking, stereotyped thinking, uncooperativeness, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation).

1.2. Magnetic resonance imaging data

All subjects underwent a single MRI scanning session using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin) located at the Sant Joan de Déu Hospital in Barcelona (Spain). Resting state functional MRI (fMRI) data was obtained using a gradient echo echo-planar (EPI) sequence depicting the blood-oxygenation-level-dependent (BOLD) contrast. Each volume contained 16 axial planes acquired with the following parameters: TR=2000 ms, TE=20 ms, flip angle=70 degrees, section thickness=7 mm, section skip=0.7 mm, in-plane resolution=3.125 x 3.125 mm. The first 10 of a total of 266 volumes acquired were discarded to avoid T1 saturation effects. Individuals were scanned while lying quietly, and they were instructed to keep their eyes open to avoid falling asleep. T1 structural images were also recorded to allow for an accurate co-registration. The

following acquisition parameters were used for these images: matrix size 512x512; 180 contiguous axial slices; voxel resolution 0.47x0.47x1mm3; echo time=3.93 ms, repetition time=2000 ms and inversion time=710 ms respectively; flip angle 15°.

1.3. Preprocessing

Images were preprocessed using the following pipeline implemented in FSL(Smith et al., 2004): 1) brain extraction in functional and structural images (FSL bet), and visual inspection to ensure correct segmentation and orientation, 2) calculation of transformation matrices in two steps: linear registration of functional to structural images in native space, and then non-linear registration to MNI template (FSL flirt and fnirt), 3) calculation of motion parameters (FSL mcflirt) and check of movement levels (allowed thresholds of maximum movement<3.0 mm and a mean movement<0.3 mm), 4) slice timing correction (FSL slicetimer), 5) high-pass temporal filtering 0.01 Hz (fslmaths), 6) linear corregistration of functional images, 7) spatial smoothing with a gaussian kernel of 8 mm full width at half maximum (fslmaths), 8) ICA-based denoising (FSL FIX, described in detail below), 9) low-pass temporal filtering at 0.25 Hz (fslmaths), and 10) spatial normalization with transformation parameters computed in step 2 (FSL convertwarp and applywarp).

1.4. Graph metrics

Before computing any graph metric, we applied a proportional (sparsity-based) threshold to remove false positives, retaining only the strongest correlations for a certain network density. To avoid the selection of an arbitrary threshold, we applied a range of thresholds which guarantees not fragmented netmats with nonrandom topological properties(Lynall et al., 2010). We selected the range of densities 0.21 – 0.35 (Figure S1). The inferior limit of the range allowed netmats to be fully connected for all subjects (i.e. node degree $k(i) > 1$ for all nodes) and the superior limit allowed netmats to retain the small world properties of the brain, e.i. higher global efficiency than lattice and lower than random netmats (Figure S1A), and higher local efficiency than random and lower than lattice netmats (Figure S1B)(Achard and Bullmore, 2007; Hadley et al., 2016). Network metrics were computed for each density within this range in segments of 0.01, and reported results are the averaged across this range.

We computed the following graph metrics with weighted networks using the Brain Connectivity Toolbox(Rubinov and Sporns, 2010):

a) Global efficiency, E^w: average of inverse shortest path length between all pairs of nodes in a network. We used the weighted variant of global efficiency described by Rubinov and colleagues(Rubinov and Sporns, 2010).

$$E^w = \frac{1}{n}\sum_{i\epsilon\, N}\frac{\sum_{j\epsilon N, j\neq i}\left(d_{ij}^w\right)^{-1}}{n-1}$$

where N is the set of all nodes in the network, n is the number of nodes, and d_{ij}^w is the shortest weighted path length between nodes i and j. Global efficiency is a measure of functional integration particularly suitable for the study of brain networks because it measures efficiency of information exchange in a parallel system(Achard and Bullmore, 2007; Latora and Marchiori, 2001).

b) Local efficiency, E_{loc}^p: global efficiency computed on the neighborhood of the node. It is a measure of functional segregation and can be considered a generalization of clustering coefficient that explicitly takes into account both direct connections and indirect paths (Latora and Marchiori, 2001). We used the weighted variant of local efficiency described by Wang and colleagues(Wang et al., 2017).

$$E_{loc}^p(i) = \frac{\sum_{j,h,j\neq h} w_{ij}w_{ih}[(\, d_{jh}^w(\tilde{\mathrm{N}}_i)]^{\,-1}}{\sum_{j,h,j\neq h} w_{ij}w_{ih}}$$

where $d_{jh}^w(\tilde{\mathrm{N}}_i)$ is the length of the shortest path between nodes j and h that contains only neighbors of node i, and w_{ij} is the connection weights between nodes defined in the subscripts.

c) Connectivity strength: average of node strength, $s(i)$ defined as the normalized sum of connectivity weights of the edges attached to each node i,

$$s(i) = \frac{\sum_{i\neq j} w_{ij}}{N-1}$$

as a measure of network connectivity(Fornito et al., 2016).

d) Degree, $k(i)$: number of edges connecting ith node to the rest of the network. Note that we computed node degree with binary netmats just to select the low limit of the range of proportional thresholds.

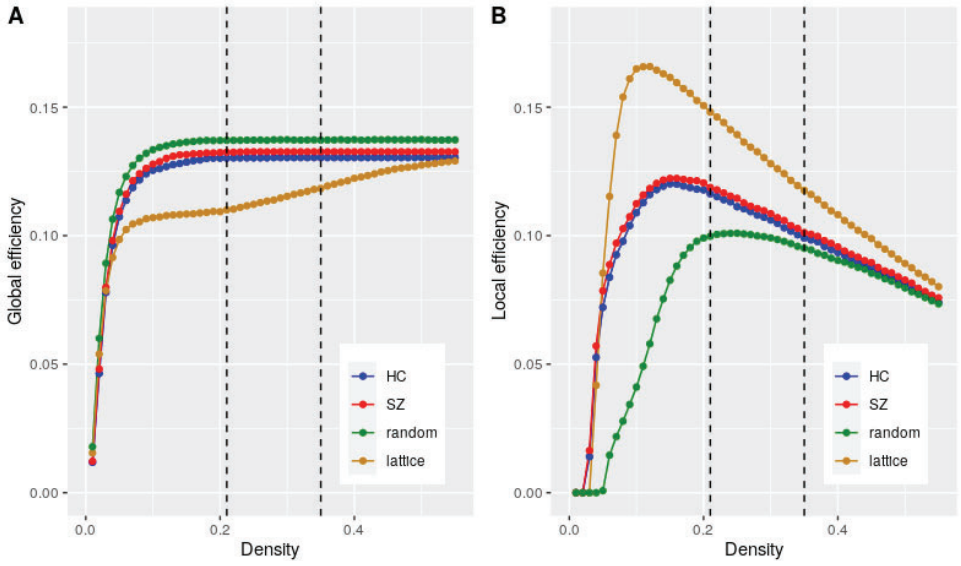

Figure S1. Global efficiency (pannel A) and local efficiency (pannel B) as a function of network density in the range 0.01 and 0.55 of strongest connection weights. Random and lattice curves were created based on 10 random and 10 lattice networks generated for each subject and threshold. Dashed vertical lines show the range of densities with non-fragmented netmats (lower limit 0.21) and small worldness topological properties (upper limit 0.35). HC, healthy controls; SZ, patients with schizophrenia. This figure should be printed in color.

2. RESULTS

2.1. Association between distance and graph metrics

At within-network level, higher variability in functional connectivity was accompanied by higher connectivity strength in both groups. Euclidean distance was correlated with connectivity strength in all networks (frontoparietal: rho_{SZ}=0.63, rho_{HC}=0.46, p<0.00001; default: rho_{SZ} =0.78, rho_{HC}=0.78, p<0.00001; dorsal attention: rho_{SZ}=0.72, rho_{HC}=0.76, p<0.00001; limbic: rho_{SZ}=0.51, rho_{HC}=0.48, p=0.0004; salience – ventral attention: rho_{SZ}=0.75, rho_{HC}=0.71, p<0.00001; somatomotor: rho_{SZ}=0.65, rho_{HC}=0.55, p<0.00001; visual: rho_{SZ}=0.61, rho_{HC}=0.58, p<0.00001). Geodesic distance was also correlated with connectivity strength in the default (rho_{SZ} =0.54, p<0.00001; rho_{HC} =0.29, p=0.037), dorsal attention (rho_{SZ} =0.37, p=0.002; rho_{HC} =0.35, p=0.007), somatomotor (rho_{SZ} =0.32, p=0.016) and salience – ventral attention (rho_{HC} =0.32, p=0.026).

Given the difference in correlations between connectivity strength and both euclidean and geodesic distances at whole-brain (rho ~ 0.95) vs within-networks (rho ~ [0.32 0.78]), we assessed the contribution of within- and between-network connections. We

recomputed connectivity strength at whole-brain level retaining only the between- or within-network connections, i.e., setting to zero the remaining connections, and then computed the correlation with distances, controlling for age, sex, premorbid IQ, current IQ and head motion. We found that correlations between connectivity strength and euclidean distance were larger in between-network (rho_{HC} = 0.98, rho_{SZ} = 0.96) than within-network connections (rho_{HC} = 0.77, rho_{SZ} = 0.6). The same pattern was observed with geodesic distance (between-network: rho_{HC} = 0.95, rho_{SZ} = 0.94; within-network: rho_{HC} = 0.76, rho_{SZ} = 0.6).

Global efficiency showed a positive correlation with Pearson's dissimilarity in frontoparietal (rho_{SZ}=0.36, p=0.004), default (rho_{SZ}=0.41, p=0.0005), dorsal attention (rho_{SZ}=0.44, p=0.0002; rho_{HC}=0.42, p=0.0004), limbic (rho_{HC}=0.40, p=0.018) and salience – ventral attention (rho_{SZ}=0.45, p<0.00001), but a negative correlation with euclidean distance in frontoparietal network (rho_{SZ}=-0.32, p=0.02).

Local efficiency showed a negative correlation with euclidean distance in frontoparietal (rho_{SZ}=-0.52, p<0.00001), default (rho_{HC}=-0.36, p=0.004), somatomotor (rho_{SZ}=-0.44, p=0.0014; rho_{HC}=-0.38, p=0.0017) and visual network (rho_{SZ}=-0.31, p=0.043). Pearson's dissimilarity was positively correlated with local efficiency in default (rho_{SZ}=0.35, p=0.004) and negatively in somatomotor (rho_{SZ}=-0.27, p=0.043). Geodesic distance was correlated with local efficiency in somatomotor network (rho_{SZ}=-0.38, p=0.001; rho_{HC}= -0.41, p=0.0011).

2.2. Effect of confounding variables

The effect of age, sex, premorbid IQ, current IQ and head motion on graph and distance metrics was assessed with a set of linear models. Given the exploratory nature of these analyses, we reported those predictors with $p < 0.01$ in the one-sample t-test with no correction for multiple comparisons.

Euclidean distance, in healthy controls, was associated with current IQ in default mode network (t(84)=-2.91, p=0.004), with age in salience ventral attention (t(84)=2.86, p=0.005), and with head motion at whole-brain (t(84)=-2.9, p=0.0048), frontoparietal (t(84)=-4.22, p=6e-5), dorsal attention (t(84)=-3.31, p=0.0014) and salience ventral attention (t(84)=-3.12, p=0.0024). No associations with euclidean distance were found in patients' group. Pearson's dissimilarity, in healthy controls, was associated with age at whole-brain (t(48)=3.6, p=0.0005) and salience ventral attention (t(84)=2.7, p=0.007), and with head motion in default (t(84)=2.6, p=0.0093). In patients, Pearson's dissimilarity was associated with female in whole-brain (t(89)=-3.02,

p=0.003), and age in limbic (t(89)=-3.06, p=0.0029). Geodesic distance, in healthy controls, was associated with head motion at whole-brain (t(84)=-3.26, p=0.0016). In patients, geodesic distance was associated with female in dorsal attention network (t(89)=-2.64, p=0.009), with head motion in somatomotor (t(89)=-2.65, p=0.009), and with premorbid IQ in patients visual (p=0.009).

Concerning graph metrics, in healthy controls, connectivity strength was negatively associated with head motion in whole-brain (t(84)=-3.57, p=0.00059), frontoparietal (t(84)=-5.01, p=3e-6), default (t(84)=-3.26, p=0.0016), dorsal attention (t(84)=-3.21, p=0.0018), limbic (t(84)=-2.871, p=0.005) and somatomotor (t(84)=-2.89, p=0.0048). No associations with connectivity strength were found in patients' group. Global efficiency was negatively associated with head motion in limbic (t(84)=-3.7, p=0.001) and somatomotor networks (t(84)=-3.14, p=0.002) in healthy controls. No significant associations were found with local efficiency in any groups.

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DISCUSSION

In the current thesis project, I addressed heterogeneity of brain function in schizophrenia. Despite the abundant evidence of functional and structural brain abnormalities in schizophrenia (15,16,19), there are no neuroimaging biomarkers of diagnostic or treatment (23,24), probably because schizophrenia disorder comprises an heterogeneous set of pathophysiological mechanisms (33,34,185). Several strategies have been used to tackle such heterogeneity: a) the assessment of clinical dimensions of psychopathology (169,235,237) or the identification of subgroups of patients based on the clinical profile (36,57,59), b) the study of behavioral constructs based on scientific knowledge of the neural circuits supporting them, such as the domains of the Research Domain Criteria framework (40,41,44), and c) the study of interindividual variability of brain structure and function, under the assumption that heterogeneous pathophysiological mechanisms should be manifested in greater heterogeneity in patients with schizophrenia (48,49,106). This thesis project presents a combination of these strategies to study functional brain abnormalities in schizophrenia.

Ecological assessment of executive functions

CMET task have been used to test the dysexecutive (frontal) hypothesis of negative symptoms, under the assumption that the lack of brain imaging evidence of the three-party association between negative symptoms severity, executive dysfunction and frontal abnormalities, might be driven by the lack of ecological validity of conventional tasks of executive functions, in analogy with the *Mesulam's frontal lobe mystery* (176). Mesulam identified some neurological patients with frontal lobe damage who showed no cognitive deficits in traditional in-lab neuropsychological tests and cognitive tasks, but severe cognitive impairment in daily life situations, and concluded that the external structured nature of office settings suppressed such behavioral impairments (238). The association between frontal (executive) dysfunction and negative symptoms in schizophrenia might be hindered by cognitive tasks used to assess executive functions. The idea of an ecological assessment of executive functions is not new (174,175,178), but the expansion of Information and Communication Technologies, with video-games and virtual reality environments, has renewed the interest in the topic (170,177).

In the first paper presented here (193), we validated the CMET task, a scanner friendly adaptation of the Modified Six Elements Test (MSET), a neuropsychological test designed to assess the self-regulation of behavior and goal management (178). Under the RDoC framework, our task design falls within the cognitive systems domain and cognitive control construct (44). Although the emphasis on the ecological nature of the task prevented for a proper discrimination of executive subdomains, it mainly involved the subconstruct of performance monitoring. CMET task was adapted to its usage in fMRI environment with clinical populations. In comparison with the original event-related task design of CMET (179,180), we adopted a block-design approach to make it well suited to assess the sustained brain activity supporting proactive maintenance and monitoring of task goals (239) as well as to use in clinical populations with executive dysfunction, since it allows a shorter task duration and functional imaging data can be analyzed even if the subject has a poor performance.

Brain imaging results in healthy participants confirmed the ability of CMET task to capture brain activations in frontoparietal (central executive) network, comprising dorsolateral prefrontal cortex, and lateral and inferior parietal regions; and cingulo-opercular (salience) network, including dorsal anterior cingulate cortex and anterior insula/frontal operculum region. Moreover, brain activation in right anterior insula was significantly correlated with task performance, and a similar trend was observed in right dorsolateral prefrontal cortex and right inferior parietal cortex. These results fully agrees with convergent evidence from fMRI and lesion studies (240–243), suggesting that high-cognitive functions arises from the dynamic interaction of distributed brain areas (214,215). Being stablished the ability of CMET task to capture brain activation associated with executive functions, particularly with goal management and tasks monitoring, we proceed to assess the brain correlates of executive dysfunction in patients with schizophrenia disorder and its association with clinical symptoms severity.

Executive dysfunction in schizophrenia

As described in the second article of the thesis, patients and controls showed overlapping maps of activation while performing the CMET task, but patients hypoactivated core regions of frontoparietal and cingulo-opercular networks, the main large-scale networks supporting cognitive control. Within frontoparietal network, we reported

reduced activation in bilateral inferior parietal, while in cingulo-opercular network, we found hypoactivations in right anterior insula/frontal operculum and anterior cingulate. These results are consistent with a previous meta-analyses of fMRI studies of executive functions (19), who reported overlapping activation maps between patients and controls, and hypoactivations in these regions.

Furthermore, we found that, in hypoactivated regions in patients, brain activation was positively correlated with task performance, even after correcting for age, sex, premorbid IQ, current IQ, antipsychotic medication and head motion. These results are in agreement with a recent meta-analysis showing that functional signal strength (e.g., beta regression coefficients in fMRI studies) within frontoparietal central executive network was positively associated with performance in executive tasks in both patients with schizophrenia and healthy controls (244). Our CMET results in healthy controls and patients with schizophrenia replicated this finding in frontoparietal and extended it into the cingulo-opercular salience network.

It is worth mentioning that Minzenberg and colleagues (19) reported a more widespread pattern of hypoactivations in patients, also including bilateral dorsolateral PFC, right ventrolateral PFC, right dorsal ACC, pre-SMA, left ventral premotor cortex, posterior areas in temporal and parietal, thalamus and putamen. Statistical power differences between our study and the aforementioned meta-analysis might explain these discrepancies. However, the absence of hypoactivations in dorsolateral prefrontal cortex seems surprising, given its relevance for cognitive control deficits in patients with schizophrenia (245,246). The overall pattern of results resonates with the control-conflict loop theory (110,218–220), that posits a dynamic processing loop between anterior cingulate cortex (ACC) / pre-supplementary motor area (pre-SMA), and dorsolateral prefrontal cortex (DLPFC). ACC/pre-SMA mediates task monitoring, identifying brain states suggestive of the necessity of cognitive control, while DLPFC exerts a direct control over the task-relevant circuits in order to make them support the ongoing goal-directed behavior. In the current study, both lateral and medial prefrontal regions were activated in controls and patients, but only medial regions showed reduced activation in all patients, i.e., dorsal anterior cingulate. These results reflect the sensibility of CMET task to impairments in the cognitive control subdomain of performance monitoring and goal management.

Analysis of intersubject variability gave us additional information to characterize the pattern of brain activation in patients. First, overlap maps were used to visualize within-group interindividual variability in brain activation maps (198). In comparison with controls, patients' overlap map had smaller values than healthy controls, suggesting that the pattern of activation was less consistent in patients. This result might be driven by either the existence of subgroups of patients with spatially distinct pattern of activation, or a reduction of activation consistent across patients (198). Subsequent analysis revealed that the data was more coherent with the second hypothesis, indicating that group differences were not driven by within-group interindividual variability in the spatial distribution of activation maps. Second, subject-specific within-group deviation maps were used to assess interindividual variability (199). In contrast with overlap maps, deviation maps allowed statistical testing on interindividual variability. Interestingly, in hypoactivated regions in patients, within-group heterogeneity significantly differed between patients and controls. Patients showed lower heterogeneity in left angular and right anterior insula. Brugger and colleagues (48,49) proposed that brain regions that show both group-level abnormalities and reduced intersubject variability in patients might point out common abnormalities across the disorder. This interpretation is particularly appealing for the anterior insula.

Anterior insula is a deep cortical region, beneath frontal lobe and operculum, located in a privileged position to play a multi-modal role. Given its pattern of structural connectivity (247,248), and its involvement in a wide variety of cognitive, affective and regulatory functions (249), it is considered an integral hub of connectivity between brain networks (214). Triple network dysfunction theory of schizophrenia posits that the interaction between default mode network and frontoparietal (central executive) networks is disrupted by aberrant signaling from the right anterior insula (228,229). Indeed, the interest in the role of anterior insula in psychopathology is growing in the field of clinical neuroscience (250). Interestingly, in a recent transdiagnostic meta-analysis of n-back studies in schizophrenia, bipolar disorder and major depressive disorder, Yaple and colleagues (251) found that bilateral anterior insula was hypoactivated in all groups of patients, supporting its key role in cognitive deficits across psychiatric diseases. The pattern of functional connectivity of insular cortex is also altered in schizophrenia. Sheffield and colleagues (252) reported reduced functional differentiation of anterior and posterior subregions of the insula, and reduced connectivity in dorsal anterior insula correlated with cognitive performance.

Concerning parietal results, our finding of patients' bilateral hypoactivations and reduced variability in left inferior parietal are consistent with its role within frontoparietal network (253). In a multi-site fMRI study, Poppe and colleagues (254) found that specific deficits in goal maintenance were associated with activity reduction in frontoparietal network, including middle frontal gyrus and left posterior parietal lobe, which might reflect connectivity deficits within frontoparietal network (231,255).

On the contrary, dorsal anterior cingulate cortex (dACC) showed greater variability in patients, suggesting the existence of functional abnormalities with heterogeneous underlying pathophysiological mechanisms (48,49) and/or the engagement of distinct compensatory mechanisms (256,257). Some authors suggested that, during cognitive control tasks, dACC serves as a 'conflict monitor', sending signals to lateral prefrontal regions when conflict is detected in order to make them implement the needed adjustments (258–261). Instead, Gratton and colleagues (110) proposed that dACC is involved in task set maintenance, instead of conflict monitoring, given the combination of transient activations at decision points of trials and sustained representations during tasks. Alternatively, dACC has also been linked to cognitive effort, conceptualized as the amplification of cognitive activity in order to address a demanding cognitive task (262). Several brain regions are involved in allocating effort, including anterior insula, lateral prefrontal cortex, intraparietal sulcus; but it is thought that dACC rests on top of the hierarchy of neural mechanisms supporting cognitive effort (263–266). Interindividual variability in any of these processes, or the combination of some of them, might explain greater heterogeneity reported in dACC in patients. However, CMET task does not allow to discriminate among them. Future studies with a proper discrimination between conflict monitoring, maintenance of task set and cognitive effort might elucidate the particular contribution of any of these processes to the observed dual pattern of hypoactivation and heterogeneity in patients with schizophrenia.

Whole-brain voxel-wise analysis on variability showed that patients had reduced intersubject variability in two clusters, comprising supplementary motor area and superior frontal gyrus. Despite that, these regions showed no activation differences relative to healthy controls, neither through voxel-wise or region-of-interest analysis. How should we interpret increased variability in the absence of activation abnormalities in patients? In order to answer that question, we conducted further ROI analyses that revealed divergent patterns of activation in these regions

depending on clinical profile. Within patients' group, activation pattern ranged from hyper- to hypo-activations. Interestingly, subgroup of patients with hypoactivation showed significantly more severe negative symptoms than those with hyperactivation, particularly apathy-avolition symptoms in superior frontal gyrus, supporting the association between motivational deficits, prefrontal abnormalities and executive dysfunction.

Motivational deficits and frontal executive dysfunction

Despite the fact that the frontal hypothesis of negative symptoms is not new (154–156), no consistent imaging evidence reported, to our knowledge, functional prefrontal abnormalities associated with executive dysfunction and apathy-avolition in schizophrenia (72,169). Early studies showed an association between negative symptoms severity and hypofrontality using PET (267–270) and SPECT (271,272). However, functional imaging evidence linking frontal abnormalities, executive dysfunction and negative symptoms have been inconsistent. Some fMRI studies found an association between prefrontal hypoactivation and negative symptoms (273), but other did not (274–278). More recently, in a fMRI study with Stroop task, Vanes and colleagues (279) found that early and chronic psychosis patients showed an inverse correlation between negative symptoms severity and brain activation in supplementary motor area and right precentral gyrus. Cerebellar abnormalities were also reported, but dependent on disease stage, since clinical symptoms severity were positively (negatively) correlated in chronic (early) psychosis, respectively. Although no dorsolateral prefrontal abnormalities were reported, cerebellar abnormalities might be driven by prefrontal-cerebellar dysconnectivity. In a resting-state fMRI and rTMS study, Brady and colleagues (280) found a causal link between negative symptoms severity and dysconnectivity between right dorsolateral prefrontal cortex and cerebellum, suggesting it as a network biomarker of negative symptoms.

One factor that might explain the lack of consistent evidence between frontal dysexecutive abnormalities and negative symptoms is the conceptualization of these symptoms. All these studies treated negative symptoms as a unitary construct, i.e., correlating global scores of negative symptoms or comparing subgroups of patients with high vs low level of negative symptoms, like the deficit syndrome category. Nevertheless, current evidence supporting the multidimensional structure of negative symptoms is solid (103–105), and preliminary evidence suggest the

involvement of distinct neural circuits in the generation and maintenance of different domains or dimensions of symptoms (169,235,237). Our results support this notion, with prefrontal hypoactivations in patients with avolition-apathy, but not diminished expressivity symptoms.

Interestingly, our data also suggest that the relationship between negative symptoms and brain activation may be non-linear. Subgroup analysis on clusters with greater intersubject variability (deviation) in patients (i.e., supplementary motor area and superior frontal gyrus) showed consistently that patients with hypoactivation (high deviation subgroup) had more severe negative symptoms, in comparison with patients with hyperactivation (low deviation subgroup). However, when activation within these clusters was correlated with negative symptoms scores in the whole sample of patients, no significant association appeared, even at uncorrected level. This result represents the opposite of what we expected under the linearity assumption for the association between brain activation in these regions and negative symptoms severity. In SMA, patients with hypoactivation (high deviation subgroup) had greater scores of negative factor, in comparison with the other groups. In contrast, in SFG, patients with hyperactivation (low deviation subgroup) had smaller scores of CAINS Map subscale that the other two groups. In both cases, the middle deviation subgroup did not show intermediate scores of negative symptoms. Note that no confound effect can explain that, since both analysis (group comparison and correlation) controlled by age, sex, premorbid IQ, current IQ and head motion. This pattern of results supports the notion that negative symptoms should be addressed neither purely dimensional nor categorical, but rather as an hybrid categorical-dimensional (106,107), which might explain divergent findings concerning persistent negative symptoms (68) or deficit syndrome (59), as well as the issues of correlation analyses to capture brain correlates of negative symptoms. In addition to statistical power or multiple comparisons correction, the hypothesized non-linear relationship might also explain the lack of significant results in the whole-brain voxel-wise correlation analysis with negative symptoms scores.

Finally, another difference between our results and Minzenberg and colleagues (19) comes from hyperactivations in patients. Minzenberg and colleagues found them in ventrolateral prefrontal cortex and midline superior frontal areas, in addition to temporal and parietal regions, insula and the amygdala. In contrast, we reported no clusters with increased activation in patients in the whole sample, but analysis of variability revealed that superior frontal

gyrus and supplementary motor area were hyperactivated in a subgroup of patients with low levels of negative symptoms. This suggests that compensatory responses are not homogeneous across patients, but rather depend on the clinical profile. Dickinson and colleagues (192) also reported different patterns of hypo- and hyper-activation in a working memory task depending on clinical symptoms. Patients with low levels of symptoms showed greater activations in right dorsolateral PFC, patients with high levels of negative symptoms showed greater activations in parietal, while patients with more distress and positive psychotic symptoms showed a widespread pattern of hypoactivation. Despite some discrepancies in the methodology, our results and Dickinson and colleagues highlight the limitations of interpreting hyperactivations (i.e., compensatory responses) in patients with schizophrenia without taking into account clinical heterogeneity.

In summary, executive dysfunction in patients with schizophrenia arises from an hypoactivation in salience network and posterior nodes of frontoparietal network. The pattern of intersubject variability in hypoactivated regions revealed distinct patterns of abnormalities within the salience network. Right anterior insula showed reduced variability in patients, which indicates a common abnormality across patients, in agreement with the triple network dysfunction hypothesis that attributes a central role to this region within the salience network to explain both disrupted large-scale communication between frontoparietal and default mode networks and the development and maintenance of psychotic symptoms in schizophrenia. On the contrary, dorsal anterior cingulate showed increased variability across patients, suggesting the existence of divergent underlying pathological or compensatory processes, consistent with the multifaceted role of this region in cognitive control. Finally, variability analysis revealed that medial prefrontal regions showed a pattern of hyper/hypoactivation depending on the severity of negative symptoms, particularly apathy-avolition and motivational deficits in superior frontal gyrus, in line with the frontal (dysexecutive) hypothesis of negative symptoms.

Intersubject variability in functional connectome

Another way to address neurobiological heterogeneity of schizophrenia disorder is to characterize and quantify interindividual variability of brain structure and function (45,47). Functional connectome, defined as the individual profile of functional connectivity, i.e., the statistical dependence of neuronal activity between brain regions computed from fMRI data (281,282), is an excellent target to study intersubject variability for two reasons. First, functional connectome is unique for each subject and stable over time (283,284). Moreover, intersubject variability in functional connectome is present in healthy population, showing a gradient of increasing heterogeneity from unimodal sensory areas to high-order multimodal associative areas (285), and shows subject-specific 'network variants' in the spatial distribution of canonical resting-state networks that appeared stable over time and related to functional task-evoked variations and behavioral correlates (286,287).

Second, the functional connectome is a large-scale description of brain connectivity dynamics, which seems to be on the appropriate scale to study brain abnormalities in schizophrenia. Nowadays, it is widely accepted that functional brain abnormalities associated with schizophrenia cannot be attributed to one unique brain region or even to one unique brain network, but rather as a consequence of the malfunctioning of both intra- and inter-network brain communication (256,288,289). Indeed, recent meta-analyses on resting-state networks and functional connectivity in schizophrenia showed strong evidence of dysconnectivity in frontoparietal, default and salience networks (15,16), suggesting that imbalanced communication between salience and both default and frontoparietal networks may underlie to core psychotic symptoms in schizophrenia (16). Moreover, in a machine learning multi-site fMRI study, Lei and colleagues (290) showed that connectome-wide functional connectivity data allowed single-subject classification of patients and controls with higher accuracy than graph metrics and whole-brain functional images, indicating that brain abnormalities in schizophrenia are better understood in terms of abnormalities in system-level functional connectivity.

Two influential theories about the etiopathology of schizophrenia pointed out into brain dysconnectivity. Friston & Frith (18) proposed that schizophrenia could be better understood in terms of a syndrome of abnormal interaction

between brain areas, mainly frontal and temporal lobes. Recently, Friston and colleagues (17) reviewed the disconnection hypothesis, concluding that the evidence for the systemic dysfunctional integration in schizophrenia is nowadays overwhelming, spanning beyond frontal and temporal lobes into a whole-brain abnormality. Another hypothesis, the triple network dysfunction theory of schizophrenia (228,229), puts the focus on the disrupted communication between frontoparietal (central executive), cingulo-opercular (salience), and default mode networks, pointing out the aberrant signaling of salience network as the source of dysconnectivity between task-positive frontoparietal and task-negative default mode networks, leading to the constellation of psychotic symptoms in schizophrenia (230,291).

In the third article of the thesis (194), we analyzed interindividual variability in the functional connectome in a large sample of chronic patients with schizophrenia and healthy controls. We found that patients with schizophrenia showed greater heterogeneity in functional connectome at whole-brain level, in agreement with previous reports (189–191). At network level, we reported greater variability in frontoparietal and default mode networks, and lower variability in salience network (at uncorrected level), suggesting divergent patterns of functional connectivity within these networks. Under the assumption that reduced variability indicates homogeneous anomalies across the disorder, our results points towards the salience network as a common source of functional dysconnectivity in schizophrenia, in agreement with the triple network hypothesis (292,293). On the contrary, frontoparietal and default mode networks appeared more heterogeneous in patients, suggestive of heterogeneous pathophysiological processes (48,49), distinct compensatory mechanisms (256), and/or non-pathological processes (257).

Nevertheless, network-level results contrast with previous studies. Chen and colleagues (190) reported greater interindividual variability in functional connectivity in visual and sensorimotor networks; and Sun and colleagues (191) reported higher variability in bilateral sensorimotor, visual, auditory and subcortical regions. Several factors might explain these discrepancies. First, we used geodesic distance to quantify intersubject variability in functional connectome, a metric that computes distance between functional connectivity matrices considering its non-euclidean geometry, and it has been recently shown that outperforms other distance metrics for subject identification using functional connectivity data (294). In contrast, previous studies (190,191) used euclidean

distance and/or Pearson's dissimilarity. Second, we addressed the issue of head motion with a different strategy than previous studies of variability. Head motion is known to have a strong influence on intrinsic functional connectivity (295). A proper preprocessing of head motion artifacts is a central step in functional connectivity analysis, since psychiatric patients usually present higher levels of head motion (296). This is particularly important for variability analysis, since it does not rely on group-averaged data. We used a three-fold strategy to control for head motion: a) discard subjects with excessive head motion, b) removal of motion artifacts through an ICA-based artifact denoising method (297,298), a method that have shown to me much more successful removing motion artifacts than nuisance regression methods, in addition to addressing other sources of noise, such as MRI susceptibility or physiological noise (299), and c) regress out of head motion (i.e., mean framewise displacement) in all statistical analyses. In contrast, previous studies used nuisance regression methods (191) or none of them (190). Indeed, geodesic distance results appeared to be robust to head motion. On the contrary, euclidean distance and Pearson's dissimilarity appeared to be head motion-dependent metrics. When we analyzed variability without head motion as covariate, we could replicate previous findings of greater variability in visual and somatomotor networks in patients, but when we included head motion as covariate, significant results disappeared. This is why we focused the discussion on geodesic distance results.

Our study assessed the association between variability in functional connectome and clinical symptoms severity, showing a negative correlation between geodesic distance at whole-brain level and PANSS total score, affective and cognitive factors. These results are consistent with Sun and colleagues (191), who reported a negative correlation between clinical symptoms severity (and disease duration) and interindividual variability in functional connectome in subcortical and posterior cortical areas. The authors interpreted these results as evidence that altered brain architecture of patients become more homogeneous as clinical symptoms increase. Nevertheless, an alternative explanation is that group average functional connectome overrepresents those patients with worst symptomatology, since those patients with higher deviation from within-group template showed less severe clinical symptoms. Similarly, in a study of variability in structural brain abnormalities in schizophrenia and bipolar disorder using normative modelling approach, Wolfers and colleagues (300) concluded that the average patient is a noninformative construct in psychiatry that collapses when mapping abnormalities at individual level. Graph theory

analysis performed on brain networks supported this interpretation, extending it into healthy controls. Group-average template of functional connectome, in both patients with schizophrenia and healthy controls, was biased towards low levels of functional integration, probably because of the incapacity of group average templates to capture the meaningful intersubject variability in the functional connectome (286,287).

Graph theory analysis also revealed that negative symptoms severity was associated with a large-scale impairment in functional integration at whole-brain level, in agreement with (301,302), but also see (303). However, a limitation should be taken into account. Negative symptoms were considered as a unitary construct in this study, while current evidence, as described above, suggest that negative symptoms is a multidimensional construct with distinct neurobiological substrates for each domain or dimension. Future studies should explore the association between negative symptoms domains and functional connectivity and topological properties of brain networks.

In summary, functional connectome in schizophrenia is highly heterogeneous, particularly for the main task-positive and task-negative networks, the frontoparietal (central executive) and default mode network, respectively; suggesting divergent pathological and/or compensatory mechanisms on these networks. On the contrary, salience network showed reduced variability in patients with schizophrenia, suggestive of a common abnormality across the disorder, in agreement with the triple network dysfunction hypothesis that attributes a central role to the salience network (right anterior insula in particular) in the large-scale connectivity abnormalities in schizophrenia. Finally, the association between intersubject variability of functional connectome and both graph metrics and clinical symptoms severity suggested that the average patient (i.e., within-group average functional connectome) overrepresents those patients with impairments in functional integration and more severe clinical symptoms.

CONCLUSIONS

1. The Computerized Multiple Elements Test (CMET) appeared to be a proper task to assess executive dysfunction, particularly goal neglect, in clinical populations. It has proven to be sensible to performance-dependent brain activation in the core networks supporting cognitive control, i.e., frontoparietal (central executive) and cingulo-opercular (salience) networks.

2. Patients with schizophrenia disorder showed CMET task performance impairments, suggestive of goal management deficits, associated with hypoactivation in the aforementioned networks. Variability analysis revealed that:

    a. Abnormalities were homogeneous across patients in right anterior insula, in line with the triple network dysfunction hypothesis, and left angular gyrus, consistent with its central role in goal management.
    b. Heterogeneous abnormalities were located in dorsal anterior cingulate cortex, in line with the multifaceted role of this region in cognitive control.

3. Correlation analyses showed no association between brain activation and negative symptoms severity, although variability analysis revealed that medial prefrontal regions were associated with divergent patterns of hypo/hyperactivation depending on negative symptoms severity, particularly with motivational deficits, supporting the dysexecutive (frontal) hypothesis of negative symptoms.

4. Functional connectome in schizophrenia appeared to be highly heterogeneous across patients, but variability was not equally distributed throughout the cortex.

    a. Frontoparietal and default mode networks showed greater variability, suggesting divergent pathological and/or compensatory mechanisms on these networks.
    b. Salience network appeared to be more homogeneous, suggesting a common abnormality across patients in this network.

5. Variability analysis on functional connectome, graph theoretical analysis of brain networks and its association with clinical symptoms suggest that patients' group-average functional connectome overrepresents functional integration impairments and clinical symptoms severity, questioning the utility of the average patient as an informative construct.

6. Results from CMET task and resting-state fMRI data, using independent samples of chronic patients with schizophrenia, converges into a common abnormality at the level of salience network, in agreement with the triple network dysfunction hypothesis that attributes a central role to the salience network (right anterior insula in particular) in the large-scale connectivity abnormalities in schizophrenia.

7. Interindividual variability analysis revealed to be a useful approach, providing additional information that would go unnoticed in the analysis of group mean, particularly about the distinction between common and heterogeneous brain abnormalities, and its promising potential to identify biological subtypes of patients with schizophrenia that allows the field to move towards 'precision psychiatry' and personalized therapeutic interventions.

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