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The neurobiology of the schizophrenia - bipolar disorder spectrum: the risk and brain mechanisms

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Summary

Abstract

Background: Schizophrenia (SCZ) and bipolar disorder (BD) are the result of complex interactions between genetic vulnerability and environmental factors, including obstetric complications, childhood traumatic experiences, exposures to social adversities and cannabis use. Converging evidence suggests that these stressors can contribute to the pathophysiology of SCZ and BD in part by causing neuroinflammation. Important information about the genetic underpinnings of SCZ and BD arises from intermediate phenotypes (IP), quantifiable biological traits that are more prevalent in unaffected relatives (REL) of patients compared to the general population and co-segregate with the disorder. Notably, neuroimaging measures can be used as IPs, as they provide a useful insight into structural and functional brain changes in individuals at familial risk for SCZ and BD that do not present the disorder, highlighting the alterations linked with the genetic risk. In addition, neuroimaging is a powerful tool to investigate brain alterations associated with the clinical manifestations of the disorders.

Methods and results: As the first step of my project, I conducted a meta-analysis of functional (fMRI) and structural magnetic resonance imaging (MRI) studies investigating REL of SCZ and BD and healthy controls (HC). A total of 230 studies on 18963 subjects (6274 SCZ REL and 7842 HC, 1900 BD REL and 2947 HC) were included. Reduced thalamic volume was present in both SCZ REL and BD REL. SCZ REL showed alterations in cortico-striatal-thalamic networks, spanning the dorsolateral prefrontal cortex and temporal regions, while BD REL showed altered cortico-thalamic and limbic regions, including the ventrolateral prefrontal, superior parietal and medial temporal cortices.

To explore whether the brain networks altered in REL were similarly affected in patients with first episode psychosis (FEP), where the effects of long-lasting exposure to medications and chronicity of the illness were not present, I performed a meta-analysis of resting state-fMRI studies in FEP (37 studies, 1554 FEP and 1481 HC). I found an increase in spontaneous activity in the bilateral striatum and superior and middle frontal gyri and a decrease in the right precentral gyrus and the right inferior

frontal gyrus compared to HC. These results were also replicated in a drug-naïve subsample. Furthermore, I examined static and dynamic functional connectivity (FC) alterations in FEP from the Human Connectome for Early Psychosis sample, an open-access database that includes imaging, clinical, cognitive and behavioral data of patients within the first five years of the onset of psychotic symptoms. We explored 96 FEP and 56 HC and found an altered static FC in FEP mainly in fronto-striatal circuits. In FEP, increased right striatum FC was associated with worse crystallized and fluid cognition evaluated with the NIH Toolbox, a multidimensional set of measures assessing cognitive, emotional, motor and sensory function. In addition, all dynamic FC parameters were altered in FEP. Then, to examine the potential influence of environmental factors on brain function in FEP, I explored the association between inflammatory markers and spontaneous brain activity in 132 FEP patients who underwent resting-state functional MRI as part of the Benefit of Minocycline on negative symptoms of schizophrenia (BeneMin) study. I observed that patients with C-reactive protein (CRP) levels ≥ 3 mg/L (indicating low level inflammation) had higher spontaneous brain activity in the right superior frontal gyrus and left cerebellum compared with FEP with CRP < 3 mg/L (indicating no inflammation). In addition, FEP with CRP ≥ 3 mg/L presented lower spontaneous brain activity in two clusters of the right postcentral gyrus and left precentral gyrus compared to FEP with CRP < 3 mg/L. We observed no relationship between measures of spontaneous brain activity and symptoms severity. However, exploratory analyses showed a negative correlation between spontaneous brain activity of the right superior frontal gyrus and verbal learning. Lastly, I aimed at exploring whether patients with chronic SCZ and BD presented similar alterations compared to individuals at familial risk and FEP. First, I collected all available evidence from the literature on dynamic FC alterations in SCZ and BD and their association with psychopathological features, that indicated a dysfunction of a triple network system underlying goal-directed behaviors and sensory networks in both disorders. Notably, in SCZ, positive and negative symptoms were associated with abnormal dynamic FC. Finally, as last step of my project, I explored spontaneous brain activity and local connectivity in a sample of individuals with chronic SCZ or BD (40 SCZ, 43 BD-I and 59 HC). The results showed a

pattern of widespread spontaneous brain activity and local connectivity alterations in patients, involving cortical and subcortical areas and the cerebellum. SCZ and BD were characterized by dysconnectivity in the prefronto-striatal circuit, as well as by alterations in the visual cortex.

Conclusions: These findings support the evidence of prefronto-striatal dysconnectity as a key neurobiological feature in the pathophysiology of the schizophrenia - bipolar disorder spectrum. In particular, changes in cortico-striatal-thalamic networks are associated with the familial risk for SCZ, while changes in cortico-thalamic and limbic regions are associated with the familial risk for BD. Individuals with manifest disorders present brain functional alterations that are mostly located in the prefronto-striatal circuit during the first phases of the disorder and tend to spread to cortical, subcortical and cerebellar regions with illness progression. SCZ and BD present overlapping and distinctive local and large-scale brain networks alterations, which can contribute to explain the similarities and the differences in the phenotypic presentations of the two disorders. Inflammation could be associated with prefrontal inefficiency in psychosis in a subgroup of patients, thus suggesting the need of stratification for this variable for tailored treatments.

CHAPTER 1: INTRODUCTION

1.1. The schizophrenia – bipolar disorder spectrum

In 1899, the German psychiatrist Emil Kraepelin postulated the dichotomy between "dementia praecox" and "manic depressive insanity", paving the way for psychiatric diagnosis of the twentieth century. According to his view, "dementia praecox" was a progressive neurodegenerative disease caused by anatomical or toxic processes that resulted in irreversible loss of cognitive functions. In contrast, he described "manic depressive insanity" as an episodic disorder that did not lead to permanent impairments in brain functions (Kraepelin E., 1987). Later in his life, Kraepelin himself admitted that this clear distinction was not applicable to a wide number of patients that presented features of both these disorders (Kraepelin E., 1921). In 1933, Dr. Jacob Kasanin first used the term of "schizoaffective psychoses" in the American Journal of Psychiatry to describe a disorder characterized by both psychotic and affective features (Kasanin, 1933). Schizoaffective psychosis was considered an intermediary diagnosis, with patients generally having better outcomes compared patients diagnosed with dementia praecox but worse than those with mood disorders. The naming of schizoaffective psychosis was the first conceptual shift toward the recognition of psychotic mood disorders and created a bridge between psychotic and mood disorders. In the following decades, alternative diagnostic frameworks have been proposed, including the idea of psychosis as a continuum that extends from unipolar to bipolar disorder (BD), schizoaffective disorder (SZA) and schizophrenia (SCZ) (Crow, 1986). This theory, first proposed in 1986, is supported by recent genetic research that has shown significant overlaps between risk genes for SCZ and BD (Prata et al., 2019).

1.2. Genetic vulnerability

In the last decades, SCZ and BD have been subjected to detailed genetic epidemiological investigation. At the beginning of the 20th century, family studies demonstrated that the incidence of SCZ was higher in relatives of patients with SCZ compared to the general population (Kallman, 1938)

and from the 1960s, twin and adoption studies played a key role in determining the familial clustering and concordance rates for SCZ (Fischer, 1973; Tienari et al., 1985). With regards to BD, early family studies showed that the risk to develop BD ranged from 3.2% to 23.4 % for offspring of bipolar patients and from 2.7% to 23% for their siblings (Tsuang et al., 2004). Current literature suggests that heritability estimates from twin and family studies range from 64 to 81% in SCZ (Lichtenstein et al., 2009) and from 60 to 85% in BD (Smoller and Finn, 2003). Recent genetic investigations have demonstrated that psychiatric disorders present significant shared genetic risk. Among these, SCZ and BD present the strongest correlation (rg = 0.60–0.68) (Anttila et al., 2018; Lichtenstein et al., 2009). The advent of genome-wide association studies (GWAS) has revolutionized the field of human quantitative genetics, generating a wealth of new information with the potential to help researchers to develop better diagnostic, prognostic, preventive and therapeutic strategies for rare and common diseases (Loos, 2020). In the field of psychiatric disorders, the great progress in genetic research has allowed to reveal the specific genetic loci associated the two disorders. Indeed, GWAS have now discovered more than 280 single nucleotide polymorphisms (SNPs) conferring risk for SCZ (Trubetskoy et al., 2022) and 64 for BD (Mullins et al., 2021), with some overlapping associations (Cardno and Owen, 2014; Ruderfer et al., 2018). Importantly, many of these common genetic variants are disorder-specific, while other forms of genetic variation, including copy number variants (CNVs) (Green et al., 2016; Marshall et al., 2017) and rare variants identified through sequencing (Courtois et al., 2020; Singh et al., 2022), appear to play a much larger role in the genetic risk for of SCZ than BD.

1.3. Environmental factors

In addition to genetic factors, environment plays a pivotal role in the pathophysiology of SCZ and BD (Robinson and Bergen, 2021). Investigations on the environmental risk factors for SCZ and BD stretches back for decades, with particular interest towards exposures in early phases of life. In particular, obstetric complications, including fetal hypoxia, maternal infections and malnutrition,

have been long considered risk factors for SCZ (Schlosser et al., 2012). Furthermore, a clear link exists between childhood traumatic experiences, such as sexual and physical abuse, parental loss, separation, neglect and bullying, and the development of psychotic symptoms (Schäfer and Fisher, 2011). In addition, later exposures to urbanicity, social adversities, migration and cannabis use are increasingly recognized as potential risk factors for SCZ and BD (Cheng et al., 2023; Heinz et al., 2013; Kaymaz et al., 2006).

Converging evidence from human and animal studies suggests that psychosocial stressors contribute to SCZ and BD pathology at least in part by increasing neuroinflammation (Comer et al., 2020). In particular, molecular studies have demonstrated that exposure to stress stimulates the sympathetic nervous system, causing the secretion of epinephrine and norepinephrine. This results in increased hypothalamic-pituitary-adrenal (HPA) axis function, which in turn leads to the release of stress hormones into the circulation (Chrousos, 2009). As a response, the organism promotes activities that contrast the stress factors, including increased cardiac function and glucose availability, while reducing less urgent processes such as digestion and immunity (Chrousos, 2009). In healthy subjects, stress-induced release of cortisol leads to the suppression of adaptive immunity and an increase in innate immunity (Barnes, 1998). Differently, in psychotic patients, cortisol seems to increase inflammatory responses instead of having anti-inflammatory effects (Comer et al., 2020). In SCZ there is evidence of altered inflammatory factors, including increased cytokines, including interleukin (IL)-6, tumor necrosis factor (TNF)-a, IL-1b, IL-12 and transforming growth factor (TGF)-b (Momtazmanesh et al., 2019). BD has been associated with increased peripheral levels of proinflammatory cytokines, such as IL-4, tumor necrosis factor-α (TNF-α), soluble tumor necrosis factor receptor 1 (sTNFR1) and sIL-2R, and this mild chronic inflammation appears to exacerbate during mood episodes (O'Brien et al., 2006).

It is noteworthy that evidence on environmental risk factors for SCZ is robust and some studies have yielded reproducible findings. Differently, in BD, fewer studies have been conducted, usually with smaller sample sizes and heterogeneous findings. Importantly, genetic and environmental factors may

not contribute in an additive manner, since the impact of an environmental exposure may depend on the genetic profile of the person exposed to the environment. These gene-by-environment interactions partly explain why only some people who experience environmental exposures associated with SCZ or BD go on to develop the disorders.

1.4. Resting-state brain activity and functional connectivity

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique that allows to explore brain activity and functional connectivity (FC) both during the performance of a task and at rest (Gregory Ashby, 2015). Differently from task-based fMRI, resting-state fMRI (rs-fMRI) is acquired in the absence of a stimulus or a task, while the participants is asked to lay still without performing any specific action (M. H. Lee et al., 2013). Rs-fMRI is based on the changes in blood oxygen level dependent (BOLD) signal, whose changes are used also for task-based fMRI, but instead of focusing on the variance explained task-related hemodynamic response, it focuses on spontaneous low frequency fluctuations (<0.1 Hz) of the signal (M. H. Lee et al., 2013). Rs-fMRI allows the estimation of several functional metrics of the brain, including FC between large-scale brain networks, spontaneous brain activity and local connectivity. In particular, FC between large-scale brain networks may be evaluated with the Independent Component Analysis (ICA), a multivariate statistical approach based on the blind source separation problem, which addresses the solution of the "cocktail party problem", which consists of separating the noises of the different speakers by using recordings of several microphones in the room (Calhoun and Adali, 2006). In fMRI, ICA decomposes the fMRI signal (time points × voxels) into a linear combination of maximally spatially independent components (ICs), that can be regarded as brain functional networks and their time-dependent expression (Du et al., 2018b). In each network, the voxels with greater Z-scores tend to have higher intra-connectivity (Calhoun et al., 2001). The mixing matrix in the decomposition includes the time course (TCs) of the ICs, where each time series reflects the temporal fluctuation of each IC, and the spatial map (SMs), related to the connectivity and degree of coengagement within a network (Allen

et al., 2011). ICA allows the simultaneous estimation of multiple networks from whole-brain data (Calhoun and Adali, 2006) and the comparison of components among subjects, allowing to capture the inter-subject variability in brain regions (Allen et al., 2011).

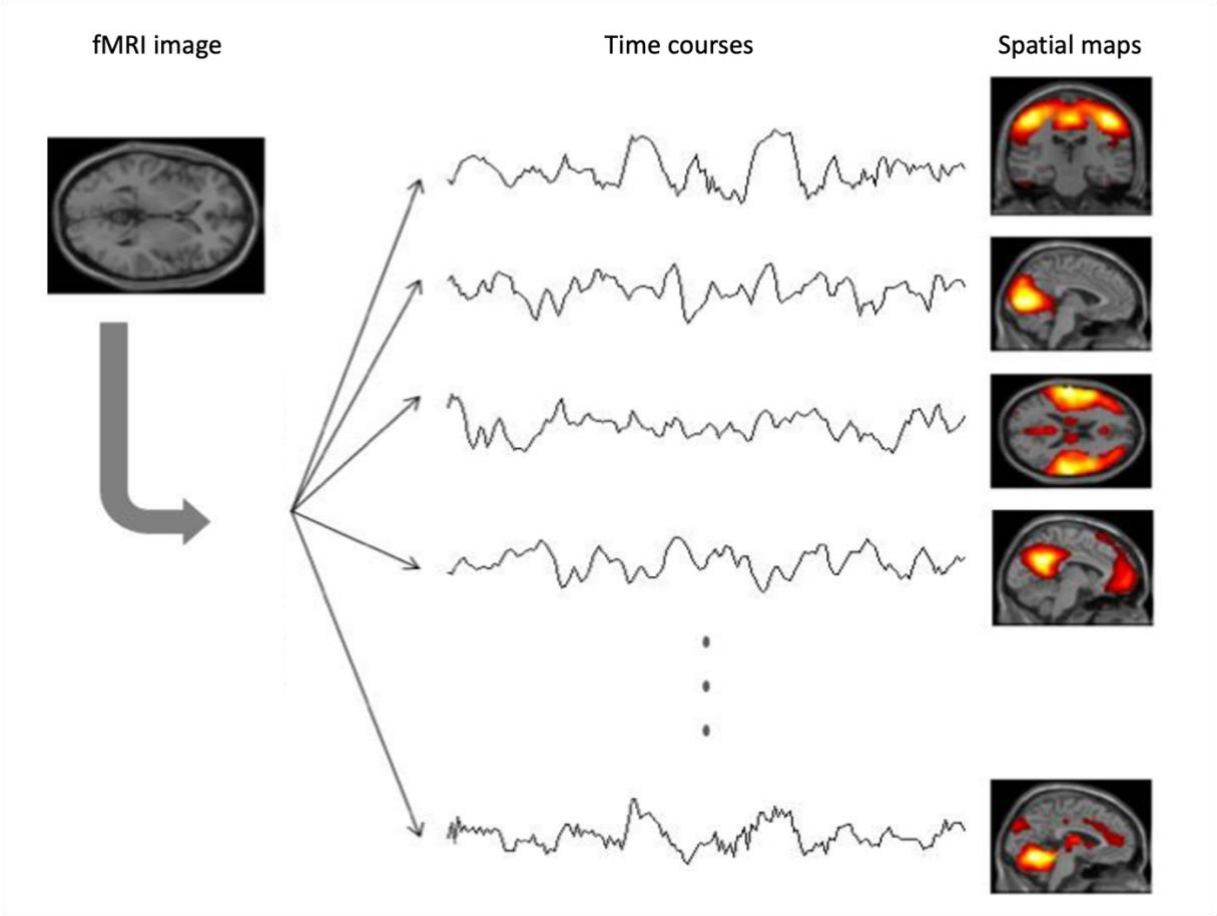

Figure 1. The ICA model assumes the fMRI signal is a linear mixture of statistically independent sources. The goal of ICA is to separate the sources into TCs and SMs.

The key idea behind ICA is to separate the fMRI signal provided by time series into a set of mutually independent and associated time courses. Each component thus represents a system of regions that show FC with each other, i.e., brain networks (Fig. 2).

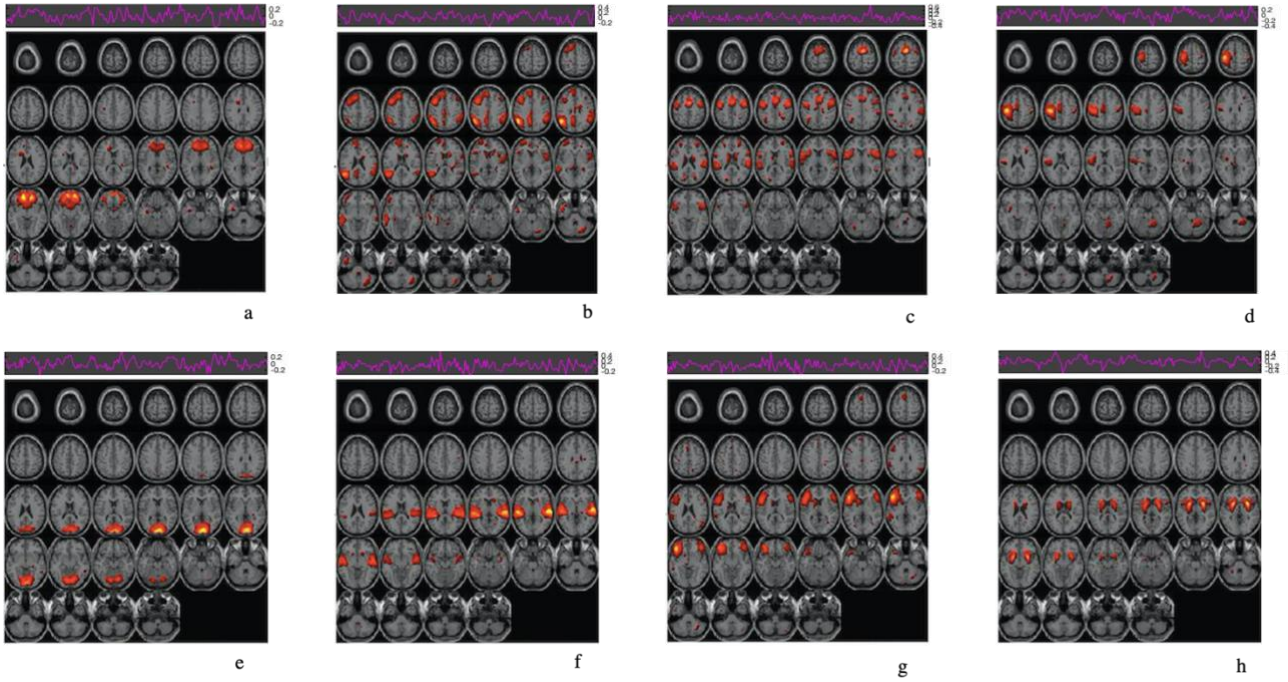

Figure 2. An example of group spatial FC maps of brain circuits obtained from spatial independent components analysis. a DMN; b executive network; c salience network; d sensorimotor network; e visual network; f auditory network; g language network; h subcortical network.

ICA also allows to examine functional network connectivity (FNC), which is calculated as the correlation between the time courses of the ICs, resulting in a connectivity matrix including connectivity strengths among all networks (Allen et al., 2011). Thus, FNC reflects temporal connectivity among different brain regions that are functionally co-activated, which is considered a measure of between-network FC (Fig. 3).

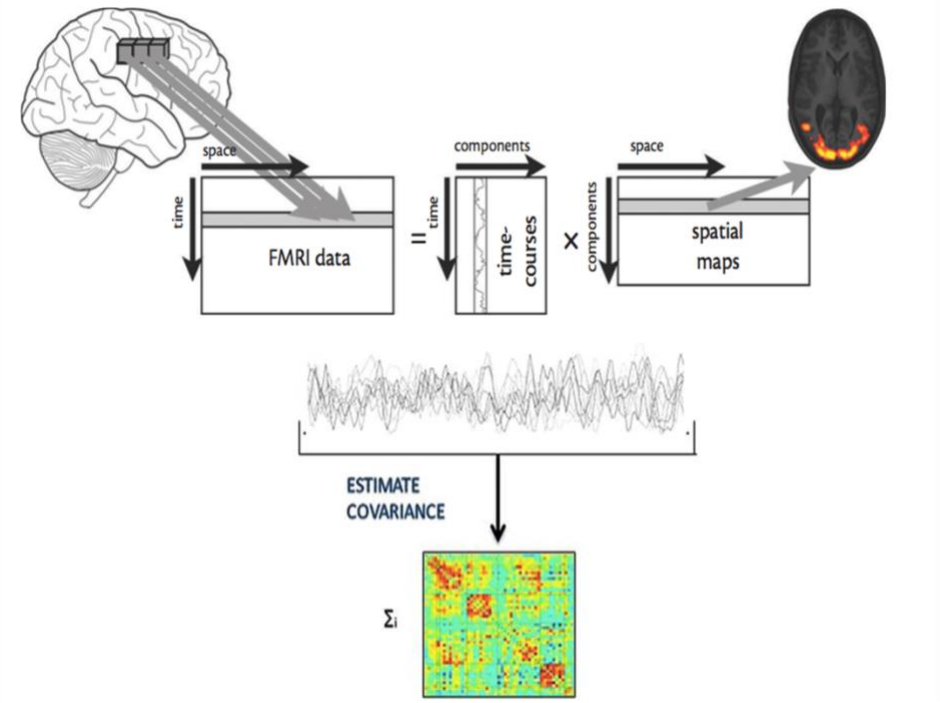

Figure 3. ICA decomposes resting-state data into ICs. TCs and SMs are calculates for each subject. FC between components is estimated as the covariance of the TCs. Adapted from Allen et al. (2014).

In addition to within and between-network FC, rs-fMRI also allows to explore the amplitude of low-frequency fluctuations (ALFF) and the fractional amplitude of low-frequency fluctuations (fALFF), measures that detect the magnitude of low frequency spontaneous fluctuations in the BOLD signal at the voxel level, which is thought to reflect spontaneous neural activity (Turner et al., 2013a). Briefly, to calculate ALFF, the time course for each voxel is band-pass filtered to select the low frequencies (0.01-0.08 Hz). Then, a fast Fourier transform is applied to convert the signal from the time to the frequency domain. Finally, ALFF is calculated as the average square root of the power spectral density of the low frequency filtered time course (Zang et al., 2007). Differently, fALFF represents the relative contribution of low frequency fluctuations to the whole detectable frequency range (0.01–0.1 Hz) (Egorova et al., 2017; Zou et al., 2008) (Fig. 4).

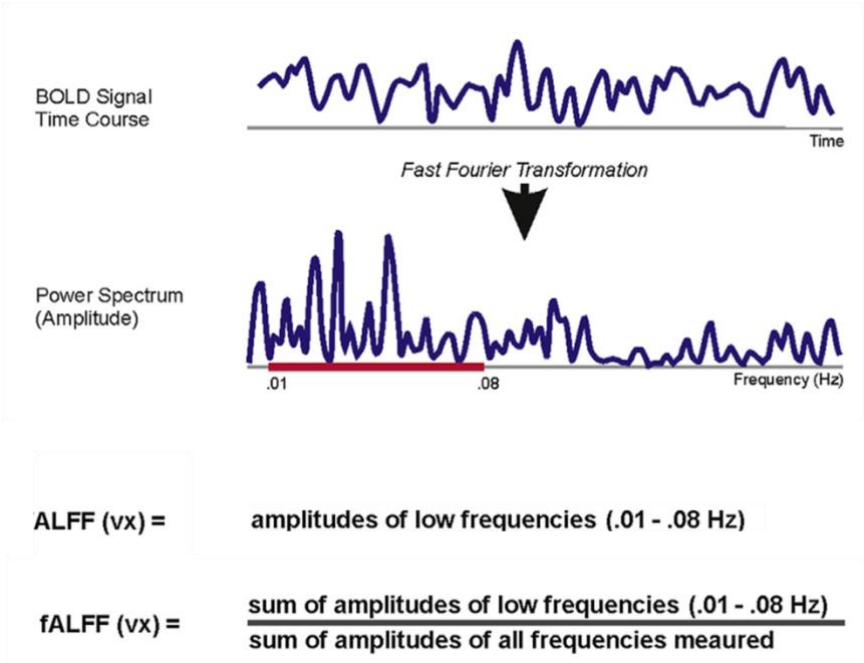

Figure 4. The BOLD signal time course is extracted for each voxel of the brain. A fast Fourier transformation is applied to the BOLD time course to convert the signal from the time to the frequency domain. ALFF values for each voxel is calculated as the average square root of the power spectral density of the low-frequency filtered time course. fALFF values for each voxel are calculated as the ratio of the sum of the sum of the amplitude values in the 0.01 - 0.08 Hz power range divided by the sum of the amplitudes over the entire power spectrum (0.01–0.1 Hz). Adapted from Haag et al. (2015)

In addition, local FC can be explored with Regional Homogeneity (ReHo), which is defined as the Kendall's coefficient concordance (KCC) between the time course of a voxel and its neighboring voxels (Zang et al., 2004). In detail, KCC can be calculated between a voxel and his face-wise neighbors (7 voxels), his face- and edge-wise neighbors (19 voxels), or his face-, edge- and node-wise neighbors (27 voxels). Values of KCC range from 0 to 1, with higher values indicating greater concordance between the activation pattern of a given voxel and that of its neighbors. Voxel-based maps are generated based on KCC values and then standardized using Z-scores to perform group analysis (Baumgartner et al., 1999; Zang et al., 2004) (Fig. 5).

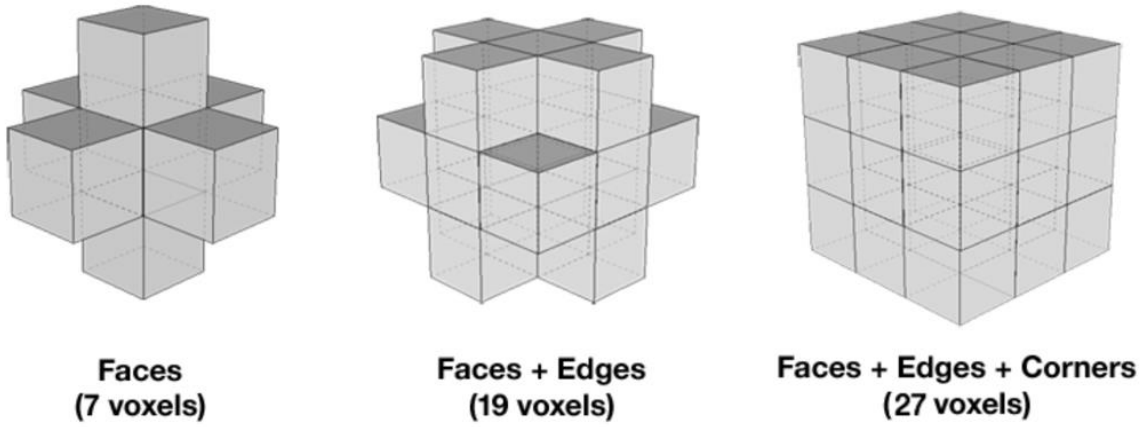

Figure 5. KCC can be calculated between a voxel and his face-wise neighbors (7 voxels), his face- and edge-wise neighbors (19 voxels), or his face-, edge- and node-wise neighbors (27 voxels).

Interestingly, ALFF, fALFF and ReHo present a strong positive relationship, suggesting that spontaneous neural activity in a voxel is accompanied by an increase in concordance of the activation pattern with its neighboring voxels (Yuan et al., 2013; Zheng et al., 2018). In addition, ALFF, fALFF and ReHo are characterized by satisfactory test-retest reliability, as well as substantial reproducibility in the gray matter compared to other global measures of brain connectivity, independent of the physiological correction method and sampling rate (Holiga et al., 2018).

1.5. Meta-analysis: coordinate-based meta-analysis and volume-based meta-analysis

Coordinate-based meta-analysis. Coordinate-based meta-analysis (CBMA) approaches, such as Activation Likelihood Estimation (ALE) and Seed-based d Mapping (SDM), allow to calculate the consistently observable effects from multiple independent neuroimaging studies (Albajes-Eizagirre and Radua, 2018; Turkeltaub et al., 2002). CBMA is employed to meta-analyze the findings of voxel-based neuroimaging studies, including fMRI and voxel-based morphometry (VBM) investigations, using the summary statistics and the coordinates of the brain areas showing a specific effect (Tench et al., 2020). As the name suggests, the inputs of the CBMA are the coordinates of all the significant peaks for every eligible contrast. In fMRI studies, the results of the CBMA reveal estimates of the distribution of activation peaks, while in VBM studies the results of the CBMA represent clusters of

voxels indicating volumetric changes (Tench et al., 2017). One of the most commonly used algorithms for CBMA is ALE, which treats foci reported in neuroimaging studies not as dimensionless points, but as spatial probability distributions centered at specific coordinates (Turkeltaub et al., 2002). ALE maps are then obtained by calculating the union of activation/volumetric changes probabilities across studies for each voxel (Turkeltaub et al., 2012). Finally, a permutation test is applied to differentiate true convergence of foci from random clustering by testing against the null hypothesis of random spatial association between experiments. Specifically, the same number of foci used in the real analysis are randomly redistributed throughout the brain and ALE maps are computed. The histogram of the ALE scores obtained from thousands of random iterations is then used to assign p values to the observed values (Eickhoff et al., 2009) (Fig. 6).

Current recommendations suggest including a minimum of 17 experiments for ALE using cluster-level family-wise error (FWE) thresholding and a minimum of 8 experiments for voxel-level FWE thresholding to control the influence of individual experiments (Eickhoff et al., 2016; Müller et al., 2018).

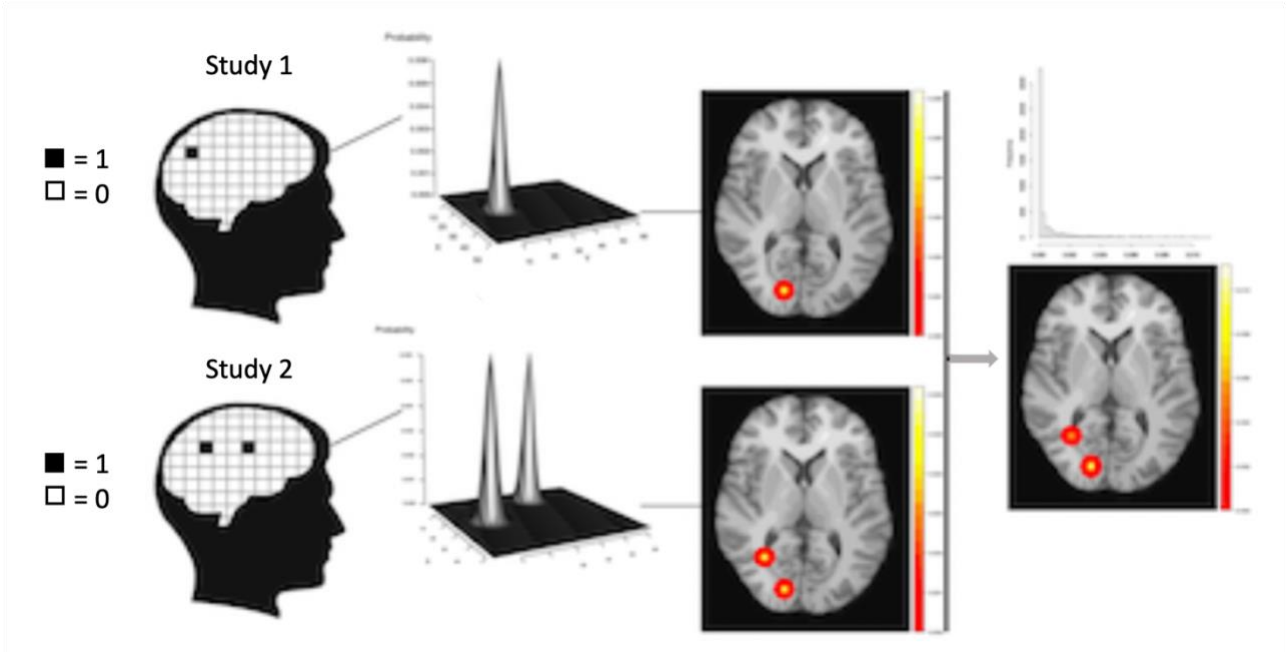

Figure 6. Illustration of ALE CBMA. Reported coordinates are first modelled by applying a Gaussian kernel. These are then combined through calculating probabilities. Adapted from Bossier et al. (2017)

One main limitation of the ALE algorithm is that it explores the spatial convergence of foci, which results in the exclusion of studies with non-significant results. To assess the robustness of CBMA results against potential publication bias, Rosenthal first proposed the "Fail-Safe N" (FSN), a measure that allows to assess the stability of meta-analytical results by describing the maximum number of studies with an effect of 0 that can be added to a meta-analysis before the conclusions are altered (Rosenthal, 1979). This concept was later adapted to the maximum number of studies with nonsignificant findings that can be added to a meta-analysis before the conclusions no longer hold (Hsu, 2010). In recent years, Acar et al. (2018) proposed a further adaptation of the FSN in CBMA using ALE, introducing an algorithm that allows assessing cluster robustness to noise and the cluster's sensitivity to publication bias. For every cluster resulting from the CBMA, the FSN can be computed, showing the number of noise studies that can be added before the cluster is no longer statistically significant (Acar et al., 2018).

Volume-based meta-analysis. Differently from CBMA, volume-based meta-analysis (VMA) are not performed on coordinates but on volumes of specific regions of interest (ROI) or on whole-brain volumes [i.e., total gray matter volume (GMV), intracranial volume (ICV), total brain volume (TBV)]. First, the standardized mean difference (SMD) effect size and its variance is computed for each study (Bakbergenuly et al., 2020). Then, for each ROI or whole-brain volume, the pooled effect size and the 95% confidence interval (CI) of the significant effect is calculated. Heterogeneity of the results of VMA is tested using Cochran's Q statistic, calculated as the sum of the weighted squared deviations of the individual study estimate from the pooled meta-analytic estimate. Then, heterogeneity is quantified using the I^2 index, calculated as $100\% \times (Q-df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom, which estimates the proportion of variability due to nonrandom differences between studies (Higgins and Thompson, 2002).

1.6. Project outline

This thesis aimed at understanding the neural correlates of the schizophrenia – bipolar disorder spectrum, spanning from the risk to the manifest disorders. In particular, we analyzed fMRI data with multimodal approaches to explore the brain changes associated with genetic and environmental risk factors for SCZ and BD and to clarify the shared and distinct alterations associated with disorders. This has been done by performing one coordinate-based and volume-based meta-analysis, one coordinate-based meta-analysis, one systematic review and by analyzing rs-fMRI data employing ICA, ALFF, fALFF and ReHo analyses.

To reach this goal, six separate studies were conducted:

Study 1: Establishing convergent neuroimaging changes associated with familial risk for SCZ and BD. In this, we explored the structural and functional alterations that are present in unaffected first- and second-degree relatives of patients with SCZ and BD in order to gain greater insight into the brain mechanisms underlying vulnerability and/or resilience to these disorders. To do so, we conducted an activation likelihood-estimation (ALE) meta-analysis of structural magnetic resonance imaging (MRI) and fMRI studies investigating brain changes associated with the genetic risk for SCZ and BD. A total of 230 studies on 18963 subjects (6274 relatives of patients with SCZ and 7842 healthy controls (HC), 1900 relatives of patients with BD and 2947 HC) were included. Our goals were to detect common brain abnormalities in subjects at genetic risk for SCZ and BD compared to HC, pinpoint disorder-specific brain abnormalities in relatives of patients with SCZ compared to relatives of patients with BD and identify differences associated with brain heritability between modalities and age.

Study 2: Establishing convergent neuroimaging changes in the early stages of patients with psychosis. In this study, to explore whether the same areas identified in the meta-analysis on individuals at genetic risk were altered also in patients with first episode psychosis (FEP), where the effects of prolonged exposure to medications and chronicity of the illness are not present, we performed an ALE meta-analysis of resting state-fMRI studies exploring spontaneous brain activity and local

connectivity in FEP (1554 FEP and 1481 HC). To explore the potential effect of age and mediations on the findings, we stratified our results according to age and medication status. We hypothesized that spontaneous brain activity and local connectivity would be altered in large-scale networks involved in higher cognitive and affective functions.

Study 3: Identification of changes of functional connectivity in the early stages of psychosis. In this study, in addition to study static FC in FEP (96 FEP, 56 HC), we also explored the patterns of FC changes across time. To do so we employed ICA and dynamic functional connectivity (DFC) analyses in the FEP sample of the Human Connectome Project for Early Psychosis. Furthermore, we wanted to explore whether FC changes were associated to crystallized and fluid cognition evaluated with the NIH Toolbox. We hypothesized that FEP would present alterations in static and dynamic FC within and between large-scale networks involved in higher cognitive and affective functions and that these changes would correlate with cognitive performances.

Study 4: Identification of the effects of environmental factors on functional connectivity in the early stages of psychosis. In this study, to examine the potential influence of environmental factors on brain function in FEP, we explored the association between inflammatory markers and spontaneous brain activity in 132 FEP patients who underwent resting-state functional MRI as part of the Benefit of Minocycline on negative symptoms of schizophrenia (BeneMin) study, a randomized, placebo-controlled, multicentric trial of 12-month minocycline. Additionally, to test the relationship between peripheral inflammation and imaging measures and symptoms severity evaluated with the Positive and Negative Syndrome Scale (PANSS), multiple regressions of PANSS scores with inflammatory markers and ALFF and fALFF values as predictors were performed. Analyses were repeated in the follow-up sample (30 minocycline, 33 placebo). Based on previous literature that identified levels of C-reactive protein (CRP) $\geq$ 3 mg/L as indicative of low-grade inflammation, individuals were stratified according to their serum levels CRP into CRP < 3 mg/L and CRP $\geq$ 3 mg/L. We expected that inflammation would affect ALFF and fALFF values and these changes would be associated with negative symptoms, however, considering the paucity of studies on the topic, we did not have specific

hypothesis on the brain areas that would be altered. Considering the anti-inflammatory properties of minocycline, we hypothesized that participants allocated to minocycline would present lower levels of peripheral inflammation and that this drug would influence the association between inflammation and spontaneous brain activity. Lastly, we aimed from one side at exploring whether patients with chronic SCZ and BD presented similar alterations compared to individuals at genetic risk and FEP, from the others to clarify the distinct and shared abnormalities between the two disorders.

Study 5: Investigation on time-varying functional connectivity changes in SCZ and BD. In study 5, we first collected all available evidence on dFC alterations in SCZ and BD and their associations with psychopathological features in order to gain a deeper understanding of the dFC changes in these disorders and their clinical significance.

Study 6: Identification of local and global changes in the intrinsic activity and connectivity changes in SCZ and BD. Lastly, in study 6, we explored spontaneous brain activity and local connectivity in a sample of chronic patients (40 SCZ, 43 BD type 1, 59 HC) by studying fALFF and ReHo. The results showed widespread spontaneous brain activity and local connectivity alterations in patients, involving cortical and subcortical areas and the cerebellum. SCZ and BD were characterized by dysconnectivity in the prefronto-striatal circuit, in addition to alterations in the visual cortex.

CHAPTER 2: THE GENETIC RISK

STUDY 1: NEURAL CORRELATES OF THE RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER: A META-ANALYSIS OF STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

2.1. Introduction

Over the past century, the Kraepelinian dichotomy between "dementia praecox" and "manic depressive insanity" has dominated clinicians' and researchers' approach to SCZ and BD. However, controversies regarding the nature of these disorders have intensified in recent years and SCZ and BD are now considered two distinct diagnosis that present similarities in the clinical presentation, but also specificities in terms of response to treatment and the course of the illness (Grande et al., 2016; Mueser and McGurk, 2004). Recent advances in genetic research have allowed to unveil the genetic architecture of the two disorders. In particular, family and twin studies have shown that both disorders have significant genetic components, with heritability estimates ranging from 60 to 80% (Nöthen et al., 2010). Furthermore, GWAS have discovered more than 280 SNPs associated with the risk for SCZ (Trubetskoy et al., 2022) and 64 for BD (Mullins et al., 2021), Importantly, recent literature has highlighted that several genes are implicated in the risk for both disorders (Gandal et al., 2018; Prata et al., 2019; Smoller et al., 2013).

Considering the genetic contribution to the risk for SCZ and BD, the study of intermediate phenotypes (IP) may help to discover brain mechanisms associated with the risk for these disorders (Preston and Weinberger, 2005). IP are quantifiable biological traits that lie in a path from gene to phenotype, present greater prevalence in unaffected REL of patients compared to the general population and co-segregate with the disorder (Preston and Weinberger, 2005). Importantly, neuroimaging research has shown that REL of patients with SCZ and BD show similar structural and functional brain alterations

to their affected relatives (Meyer-Lindenberg and Weinberger, 2006; Tost et al., 2010). Crucially, IP are not confounded by factors related to the disease, including medication use, chronicity of the disorder, medical and psychiatric comorbidities, smoking and substance abuse (Rasetti and Weinberger, 2011). Therefore, the study of IP in REL of patients with SCZ or BD can help elucidating the brain mechanisms underlying both vulnerability and resilience to the disorders.

Within IP, neuroimaging measures are closer to genes and may therefore provide greater insight into the pathophysiology of the disorders. In the last years, several MRI and fMRI investigations have been conducted in REL (Cao et al., 2016; Cattarinussi et al., 2019; Ivleva et al., 2013; Rasetti et al., 2011; Saarinen et al., 2020; Scognamiglio and Houenou, 2014; Zhang et al., 2020). Additionally, multicenter neuroimaging consortia have allowed to explore brain alterations in large samples of REL. In particular, the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA)-Relatives Working Group described an increase in intracranial volume (ICV) in relatives of BD (BD-REL) compared to healthy controls (HC), while relatives of SCZ (SCZ-REL) showed reduced total brain, cortical gray matter (GM), cerebral white matter, cerebellar gray and white matter and thalamic volumes (de Zwarte et al., 2019). Our research group and Zhang et al. (2020) showed that BD-REL presented volumetric alterations in the right superior frontal gyrus (SFG), right inferior frontal gyrus (IFG), left superior temporal gyrus (STG), left supramarginal gyrus, right gyrus rectus and right cerebellum, in addition to hyperactivation in the right IFG, left STG, left middle temporal gyrus (MTG), right caudate and right dorsal anterior cingulate cortex (ACC) during cognition, hyperactivation in the right amygdala during emotional processing and in the right orbitofrontal cortex during reward tasks (Cattarinussi et al., 2019; Zhang et al., 2020). Differently, a meta-analysis of fMRI studies in SCZ-REL reported an hyperactivation in the right IFG, MTG, STG, inferior parietal lobule (IPL), precuneus, caudate and left precentral gyrus and decreased activation in the right ACC during cognitive tasks, and an increased activation in the left parahippocampal gyrus (PHG) during emotive paradigms (Scognamiglio and Houenou, 2014).

It is however important to notice that the existing neuroimaging literature on REL is affected by considerable heterogeneity both in terms of included populations and MRI methods. Moreover, only few studies directly compared SCZ-REL and BD-REL, resulting in a gap of knowledge about the differences in terms of brain volumetric and functional alterations between these at-risk populations. ENIGMA mega-analyses on REL have partially helped overcome these limitations, by offering the opportunity of analyzing data from a large number of subjects using the same processing strategy, even when the individual site results are negative (Zugman et al., 2022). However, they only explored differences between REL and HC in structural regions of interest (ROI). Differently, coordinate-based meta-analysis (CBMA) methods can include both structural and functional studies without an a priori selection of brain regions and are not limited to the data shared by the authors that are part of the consortium. Therefore, CBMA and ENIGMA represent two different approaches that may provide complementary information.

In this systematic review and meta-analysis, we summarized and analyzed the available evidence on brain activation and volume differences in SCZ-REL and BD-REL to identify the brain mechanisms underlying vulnerability for these disorders using both a voxel-based and a volume-based approach. Our overarching goals were: 1) detecting common brain abnormalities in SCZ-REL and BD-REL compared to HC; 2) identifying disorder-specific brain abnormalities in SCZ-REL compared to BD-REL; 3) pinpointing differences associated with brain heritability between modalities and age.

2.2. Methods

2.2.1. Article selection and classification

In October 2020, we conducted a search on PubMed, Scopus, and Web of Science of the original papers published in peer-reviewed journals without any language restriction, following the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) (Brooke et al., 2021). We used a combination of the following keywords: “schizophrenia” OR “bipolar disorder” AND

"relative" OR "genetic risk" OR "first-degree relatives" OR "twins" OR "offspring" OR "parents" OR "high risk" OR "genetic risk" OR "liability" OR "family study" AND "VBM" OR "fMRI" OR "magnetic resonance imaging" OR "MRI" OR "voxel-based morphometry" OR "cortical thickness". We also included relevant investigations appearing in the reference lists of the articles included in the meta-analysis. Studies were included if they: 1) were case-control studies; 2) included a group of unaffected first or second-degree REL of patients with SCZ or BD, matched for age and gender with a group of HC; 3) employed functional and/or structural magnetic resonance imaging; 4) reported stereotaxic coordinates of the difference in brain volume or activation between REL and HC; 5) analyzed whole-brain activation, whole-brain volume or ROI volumes. Exclusion criteria were the following: 1) studies that investigated only functional connectivity; 2) functional ROI studies; 3) studies exploring white matter; 4) studies that found no differences in activation or brain volumes with a VBM approach between REL and HC.

The initial search resulted in 4139 articles. After removing duplicates and reviewing the abstracts of these articles, 683 studies were selected for full-text reading. 453 studies were also excluded because: 1) there were no statistically significant differences in brain activation or volume in the VBM studies between REL and HC; 2) REL of SCZ and BD patients were analyzed together; 3) the studies investigated subjects with unipolar and bipolar depression; 4) parametric effects were evaluated. A total of 230 studies were selected (Fig.7).

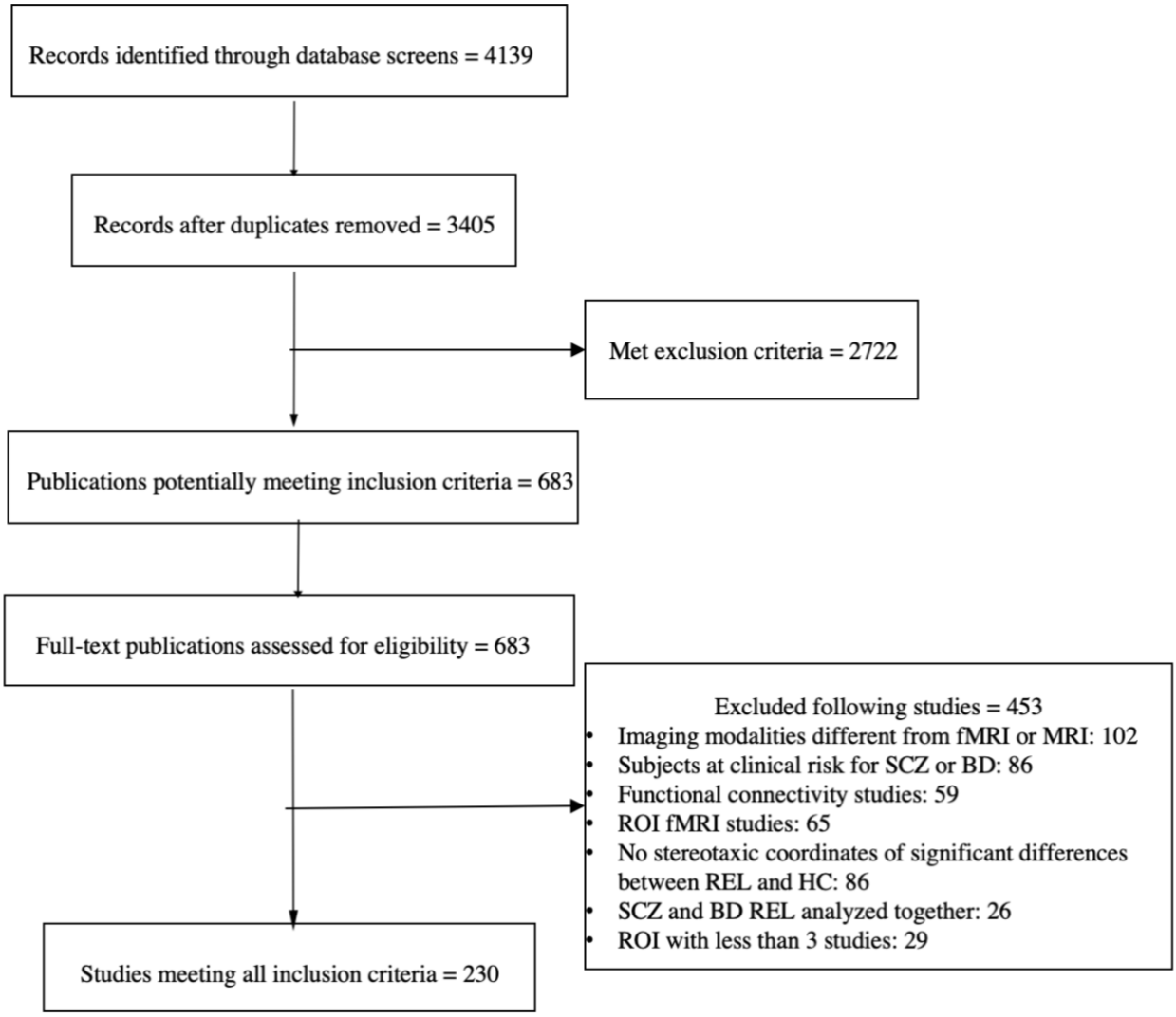

Figure 7. PRISMA flowchart for the meta-analysis of imaging articles in SCZ-REL and BD-REL. Each selected article could include multiple volumetric measures that were considered as individual studies.

The included studies had the following characteristics:

- 59 fMRI studies on 1461 SCZ-REL (mean age 30.3 years) and 1908 HC (mean age 28.5 years). Task-based fMRI included cognitive (n=39) (Altamura et al., 2012; Avsar et al., 2011; Becker et al., 2008; Bonner-Jackson et al., 2007; Brahmbhatt et al., 2006; Callicott et al., 2003a; Choi et al., 2012; de Leeuw et al., 2013; Delawalla et al., 2008; Di Giorgio et al., 2013; Diwadkar et al., 2014; Filbey et al., 2008; S. Jiang et al., 2015; Karch et al., 2009; Keshavan et al., 2002b; Landin-Romero et al., 2015; A. Lee et al., 2019; Li et al., 2016, 2007; Liddle et al., 2013; Loeb et al., 2018; Lopez-Garcia et al., 2016; MacDonald et al., 2006; McAllindon

et al., 2010; Oertel et al., 2019; Pirnia et al., 2015; Rasetti et al., 2014; Sambataro et al., 2013; Seidman et al., 2007, 2006; Sepede et al., 2010; Stäblein et al., 2019; Stolz et al., 2012; Thermenos et al., 2013, 2007, 2004; Whitfield-Gabrieli et al., 2009; Whyte et al., 2006), affective (n=12) (Hart et al., 2015, 2013; H. J. Li et al., 2012; Lo Bianco et al., 2013; Nook et al., 2018; Park et al., 2016; Pulkkinen et al., 2015; Spilka et al., 2015; Spilka and Goghari, 2017; van Buuren et al., 2012; Van Meer et al., 2014; Venkatasubramanian et al., 2010) and reward paradigms (n=4) (De Leeuw et al., 2015; Grimm et al., 2014; Gromann et al., 2014; Hanssen et al., 2015). The other 4 studies employed different tasks (Dodell-Feder et al., 2014; Herold et al., 2018; Raemaekers et al., 2006; Rajarethinam et al., 2011);

- 22 fMRI studies on 557 BD-REL (mean age 27.0 years) and 1086 HC (mean age 27.1 years). Task-based fMRI included cognitive (n=13) (Allin et al., 2010; Alonso-Lana et al., 2016; Drapier et al., 2008; Frangou, 2012; Kim et al., 2012; Pagliaccio et al., 2017; Pompei et al., 2011; Roberts et al., 2013; Sepede et al., 2012; Sugihara et al., 2017; Thermenos et al., 2011, 2010; Tseng et al., 2015), affective (n=7) (Chan et al., 2016; Chang et al., 2017; Kanske et al., 2015; Manelis et al., 2015; Olsavsky et al., 2012; Surguladze et al., 2010; Wiggins et al., 2017), and reward paradigms (n=2) (Linke et al., 2012; Manelis et al., 2016);
- 15 VBM whole brain studies on 925 SCZ-REL (mean age 27.1 years) and 1041 HC (mean age 29.1 years) (Chang et al., 2016; Guo et al., 2015, 2014; Honea et al., 2009; Hu et al., 2013; Ivleva et al., 2017; Job et al., 2003; X. Li et al., 2012; Lui et al., 2009; Marcelis et al., 2003; Oertel-Knöchel et al., 2012; Sugranyes et al., 2015; Tian et al., 2011; Wagshal et al., 2014);
- 11 VBM whole brain studies in 282 BD-REL (mean age 29.1 years) and 373 HC (mean age 29.1 years) (Eker et al., 2014; Frangou, 2012; Hajek et al., 2013; Hanford et al., 2016; Kempton et al., 2009; Lin et al., 2015; Manelis et al., 2016; Matsubara et al., 2016; Matsuo et al., 2012; Sariçiçek et al., 2015);
- 53 ROI studies on 2146 SCZ-REL (mean age 31.4 years) and 2733 HC (mean age 28.5 years). ROI studies included the amygdala (n=20) (Bhojraj et al., 2011; De Zwarte et al., 2019;

Dougherty et al., 2012; Goghari et al., 2011; Keshavan et al., 2002a; Keshavan et al., 1997; Lawrie et al., 2001; O'Driscoll et al., 2001; Rich et al., 2016; Seidman et al., 1999, 1997; Şişmanlar et al., 2010; Staal et al., 2000), the amygdala-hippocampal complex (n=3) (Keshavan et al., 2002a; Lawrie et al., 2001; O'Driscoll et al., 2001), the hippocampus (n=39) (Arnold et al., 2015; Baaré et al., 2010, 2001; Bois et al., 2015; Collip et al., 2013; De Zwarte et al., 2019; Dougherty et al., 2012; Ebner et al., 2008; Francis et al., 2013; Goghari et al., 2011; Ho and Magnotta, 2010; Karnik-Henry et al., 2012; Keshavan et al., 1997; McDonald et al., 2006; Pirnia et al., 2015; Rich et al., 2016; Roalf et al., 2015; Schulze et al., 2003; Seidman et al., 2014, 2002, 1999, 1997; Staal et al., 2000; Tepest et al., 2003; Van Erp et al., 2004; Van Haren et al., 2004; Wood et al., 2005), the caudate (n=18) (De Zwarte et al., 2019; Dougherty et al., 2012; Ettinger et al., 2012; Knöchel et al., 2016; Lawrie et al., 2001, 1999; Oertel-Knöchel et al., 2012; Rich et al., 2016; Roalf et al., 2015; Seidman et al., 1999, 1997; Staal et al., 2000), the striatum (n=15) (De Zwarte et al., 2019; Dougherty et al., 2012; Lawrie et al., 2001, 1999; Oertel-Knöchel et al., 2012; Rich et al., 2016; Roalf et al., 2015; Seidman et al., 1999, 1997), the thalamus (n=18) (De Zwarte et al., 2019; Ettinger et al., 2007; Harms et al., 2007; Knöchel et al., 2016; Lawrie et al., 1999; Oertel-Knöchel et al., 2012; Rich et al., 2016; Roalf et al., 2015; Seidman et al., 1999, 1997; Şişmanlar et al., 2010) and the pituitary gland (n=4) (Collip et al., 2013; Cullen et al., 2015; Mondelli et al., 2008; J. L. Shah et al., 2015);

- 22 ROI studies on 694 BD-REL (mean age 27.7 years) and 1837 HC (mean age 27.1 years). They included the amygdala (n=14) (Akbaş et al., 2017; Bauer et al., 2014; Bechdolf et al., 2012; Bootsman et al., 2015; Hajek et al., 2009; Karchemskiy et al., 2011; Lancaster, 2018; Noga et al., 2001; Papmeyer et al., 2016; Park et al., 2015; Roberts et al., 2020; Sanches et al., 2019; Sandoval et al., 2016; Singh et al., 2008), the hippocampus (n=13) (Akbaş et al., 2017; Arnold et al., 2015; Bauer et al., 2014; Bootsman et al., 2015; Hajek et al., 2009; Karchemskiy et al., 2011; Lancaster, 2018; McDonald et al., 2006; Noga et al., 2001;

Papmeyer et al., 2016; Roberts et al., 2020; Sanches et al., 2019; Van Erp et al., 2004), the caudate (n=7) (Bauer et al., 2014; Bootsman et al., 2015; Hajek et al., 2009; Lancaster, 2018; Noga et al., 2001; Papmeyer et al., 2016; Roberts et al., 2020), the striatum (n=7) (Bauer et al., 2014; Bootsman et al., 2015; Lancaster, 2018; Noga et al., 2001; Papmeyer et al., 2016; Roberts et al., 2020; Singh et al., 2008), the thalamus (n=7) (Akbaş et al., 2017; Bootsman et al., 2015; Karchemskiy et al., 2011; Lancaster, 2018; Papmeyer et al., 2016; Roberts et al., 2020; Singh et al., 2008) and pituitary gland (n=3) (Hajek et al., 2008; Mondelli et al., 2008; Takahashi et al., 2010);

- 68 whole brain volumetric studies in 3003 SCZ-REL (mean age 34.9 years) and 3915 HC (mean age 31.2 years), including total GMV (n=26) (Boos et al., 2012; Brans et al., 2008; De Zwarte et al., 2019; Gogtay et al., 2003; Ho, 2007; Honea et al., 2008; Hulshoff Pol et al., 2012, 2004; Lei et al., 2015; Marcelis et al., 2003; Rich et al., 2016; Sharma et al., 1998; Staal et al., 2000; Sugranyes et al., 2015; van Haren et al., 2020; Yang et al., 2010), intracranial volume (n=25) (Baaré et al., 2001; Boos et al., 2012; Cannon et al., 1998; De Zwarte et al., 2019; Francis et al., 2013; Goghari et al., 2007; Hulshoff Pol et al., 2012, 2004; Jou et al., 2005; Keshavan et al., 2002a; Oertel et al., 2010; Park et al., 2013; Rajarethinam et al., 2004; Sugranyes et al., 2015; Van Erp et al., 2004; van Haren et al., 2020) and whole brain (n=56) (Baaré et al., 2010; Boos et al., 2012; Brans et al., 2008; De Zwarte et al., 2019; Dougherty et al., 2012; Ebner et al., 2008; Ettinger et al., 2007; Frangou et al., 1997; Gogtay et al., 2003; Hanford et al., 2016; Harms et al., 2007; Hulshoff Pol et al., 2012, 2004; Keshavan et al., 2002b; Keshavan et al., 1997; Lawrie et al., 2001, 1999; Lei et al., 2015; Marcelis et al., 2003; McDonald et al., 2006, 2002; Mcintosh et al., 2011; Mondelli et al., 2008; Noga et al., 1996; Owens et al., 2012; Pirnia et al., 2015; Rajarethinam et al., 2007; Seidman et al., 2014, 2002, 1999, 1997; Staal et al., 2000; Sugranyes et al., 2015; van der Velde et al., 2015; van Haren et al., 2020; Van Haren et al., 2004; Wood et al., 2005; Yan et al., 2019; Yang et al., 2010);

- 29 volumetric studies of the whole brain in 883 BD-REL (mean age 39.1 years) and 1320 HC (mean age 35.3 years), which explored total GMV (n=14) (Bearden et al., 2011; Hajek et al., 2013, 2009, 2008; Hulshoff Pol et al., 2012; Karchemskiy et al., 2011; Kieseppä et al., 2003; Lu et al., 2019; Matsuo et al., 2012; Nery et al., 2015; Sugranyes et al., 2015; Van Der Schot et al., 2009; van Haren et al., 2020), intracranial volume (n=12) (Bauer et al., 2014; Bootsman et al., 2015; Hajek et al., 2010, 2008; Hanford et al., 2016; Hulshoff Pol et al., 2012; Kempton et al., 2009; Singh et al., 2008; Sugranyes et al., 2015; Takahashi et al., 2010; Van Der Schot et al., 2009; van Haren et al., 2020) and whole brain (n=14) (Akbaş et al., 2017; Bearden et al., 2011; Hajek et al., 2013; Hulshoff Pol et al., 2012; Karchemskiy et al., 2011; Kieseppä et al., 2003; Matsuo et al., 2012; McDonald et al., 2006; Mondelli et al., 2008; Noga et al., 2001; Park et al., 2015; Van Der Schot et al., 2009; van Haren et al., 2020).

Fifteen studies [Sharma (1998), Baarè (2001), McDonald (2002), Seidman (2002), Callicot et al. (2003), Schulze (2003), Hulshoff Pol (2004), Van Erp (2004), Van Haren (2004), McDonald (2006), Yang (2010), Hajek et al. (2012), Guo et al. (2014), Lei (2015), De Zwarte (2018)] were treated as independent studies as they reported data from two or more different cohorts.

Considering the influence of neurodevelopmental processes on neuroimaging findings and the potential confounding effect of age, we decided to stratify the meta-analysis according to the age of participants: if both samples in a study had a mean age ≤ 18 years, the population was classified as adolescent REL, otherwise it was classified as adult REL. Of the included studies, 5 fMRI, 2 VBM, 9 ROI and 8 whole-brain volumetric studies were performed in adolescent SCZ-REL, and 9 fMRI, 3 VBM, 5 ROI and 9 whole-brain volumetric studies were performed in adolescent BD-REL. Among BD-REL studies, 9 fMRI and 6 VBM studies were conducted only in REL of patients affected by bipolar disorder type I (BD-I-REL). Other investigations were conducted either in mixed samples of BD-I-REL and bipolar disorder type II REL (BD-II-REL) or in REL of BD probands with no further details about their diagnosis. Details of the included studies are reported in the Appendix.

2.2.2. Quality assessment

All studies were evaluated for quality with an Imaging Methodology Quality Assessment Checklist (adapted from Strakowski et al., 2000) on the following parameters: subjects, imaging acquisition and analysis, results and conclusions (Strakowski et al., 2000). Only two studies showed a low quality (Noga et al., 1996, 2001).

2.2.3. Coordinate-based meta-analysis

A total of 24 CBMA were performed. First, we performed a global CBMA on all fMRI studies. Secondly, we conducted a CBMA on each type of fMRI tasks (cognitive, affective and reward). Third, we performed a CBMA on adolescent REL and adult REL. Similarly, for VBM studies we first performed a global CBMA of all available studies and then two CBMA on adolescent REL and adult REL. In addition, we reran two CBMA focusing specifically on BD-I-REL (9 fMRI and 6 VBM studies). Finally, to remove the effects of comorbidities and small sample sizes, we repeated the CBMA including only the studies with RELs without psychiatric disorders (unaff-REL) and with a population equal or greater than 10 (REL-n≥10). To explore areas of convergent abnormalities between fMRI and VBM investigations, we performed a unified all-effects CBMA for SCZ-REL, BD-REL and SCZ- REL and BD-REL pooled together.

CBMA included only the contrasts that resulted in a significant difference between REL and HC (REL>HC and/or REL<HC) using the activation likelihood estimation (ALE) method (GingerALE 3.0.2). ALE meta-analyses were performed using the algorithm revised by Eickhoff et al. (2009) and Turkeltaub et al. (2012) (Eickhoff et al., 2009; Turkeltaub et al., 2012). Significance was assessed using a cluster-level p(FWE)=0.05 thresholding with a cluster forming threshold of p=0.001 for n≥17 studies and a voxel-level p(FWE)=0.05 thresholding for 8≤n<17 studies, respectively (Eickhoff et al., 2016; Müller et al., 2018). For completeness, we also conducted exploratory analyses for the contrasts with fewer than 8 experiments. To assess the effect of negative studies, we performed a simulation

by adding to our meta-analyses noise studies that reported foci randomly distributed throughout the brain (Acar et al., 2018). The number of noise studies was equal to the number of studies that were retrieved in the initial search but were then excluded because they did not report a significant difference in function/volume between REL and HC.

2.2.4. Volume-based meta-analysis

We performed a VMA on specific regions of interest (ROI) and on whole-brain volumes [total gray matter volume (GMV), intracranial volume (ICV), total brain volume (TBV)] using Jamovi. Volume (mean and standard deviation), number of participants and demographic data (age and gender) were extracted for each study. A volume entered a meta-analysis when a minimum of three studies met the inclusion criteria (SCZ-REL: amygdala, amygdala-hippocampal complex, caudate, hippocampus, pituitary, striatum thalamus; BD-REL: amygdala, caudate, subgenual cingulate, hippocampus, striatum, thalamus and pituitary gland). ICV was defined as the sum of gray matter, white matter and cerebrospinal fluid volumes, while TBV was calculated as the sum of gray and white matter volumes. First, we calculated the standardized mean difference (SMD) effect size and its variance for each study. Then, for each volume, we calculated the pooled effect size and the 95% confidence interval (CI) of the effect of kinship with each group of patients using a random-effects model. Statistical significance of the overall effect size was evaluated using a Z-test, with a threshold of $p< 0.05$. Heterogeneity was tested using Cochran's Q statistic and quantified using the I^2 index. A set of outlier analyses using dmetar in R was performed to exclude studies contributing to heterogeneity. Lastly, we conducted a network random-effects meta-analysis to compare the SMD of SCZ-REL and BD-REL for each VMA using netmeta in R.

2.2.5. All-effect meta-analyses

As ALE operates independently of the direction of the effect, all-effect meta-analyses were conducted to concatenate foci from different experimental contrasts to 1) combine findings of increased and

decreased activation or volume, and 2) combine findings from fMRI and VBM. Separated all-effects meta-analyses were conducted for SCZ-REL and BD-REL.

2.3. Results

2.3.1. Functional coordinate-based meta-analysis

SCZ-REL. In the global and adult fMRI CBMA, SCZ-REL had an hyperactivation in the right dorsolateral prefrontal cortex (DLPFC, BA6/9). In addition, adult SCZ-REL presented an increased activation in the right ACC, right DLPFC and right BA10 compared to HC. During cognitive tasks SCZ-REL showed an increased activation in the right DLPFC. No differences were found in emotion paradigms. Exploratory analyses on reward studies showed a reduced activation in the ventral caudate in SCZ-REL compared to HC (Fig. 8). Results were similar in REL-n≥10 and unaff-SCZ-REL.

BD-REL. In the global fMRI CBMA, BD-REL had an increased activation in the right PHG/uncus and decreased activation in the left precuneus compared to HC. Exploratory analyses showed that BD-REL presented reduced activation in the bilateral superior parietal lobule (SPL) and the left postcentral gyrus during cognitive tasks, along with increased activation in the right parahippocampal gyrus (PHG)/uncus and left ACC/mPFC during emotion processing compared to HC (Fig. 8), respectively. Exploratory CBMA demonstrated that adult BD-REL had an increased activation in the left ACC/mPFC and lower activation in the bilateral SPL and left postcentral gyrus compared to HC, while BD-I-REL showed higher activation in the right posterior cingulate cortex (PCC) and the right anterior prefrontal cortex (aPFC), and lower activation in bilateral SPL and left post-central gyrus during cognitive tasks. All studies were REL-n≥10.

BD-REL vs. SCZ-REL. BD-REL presented a higher activation in the right ventrolateral prefrontal cortex (VLPFC)/BA13 and right PHG compared to SCZ-REL.

Adding noise studies did not change the results in all CBMAs.

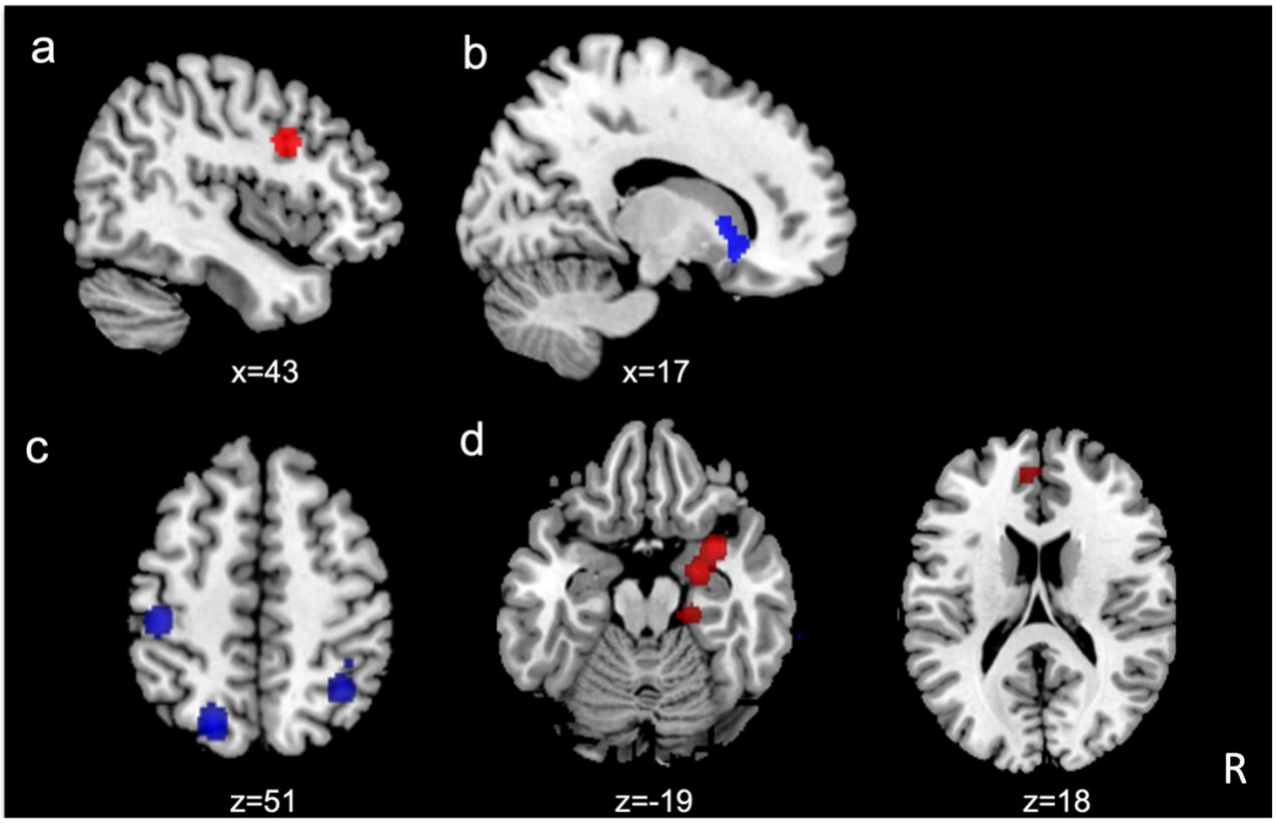

Figure 8. CBMA of neural activity alterations in SCZ-REL compared with HC during cognitive (a) and reward tasks (b) and in BD-REL compared with HC during cognitive (c) and affective tasks (d). Increased and decreased functional activation in REL compared to HC is shown in red and blue, respectively. All images are thresholded with $p<0.005$ and a spatial extent of 10 voxels. Fig. b, c and d represent the results of exploratory analyses. R = right.

2.3.2. Volumetric coordinate-based meta-analysis

SCZ-REL. SCZ-REL presented reduced GMV in the left middle temporal gyrus (MTG) compared to HC. These results were replicated in adult REL and in REL-n≥10 (Fig. 9).

BD-REL. BD-REL had lower GMV in the left temporo-parietal junction (TPJ), right medium-CC and right PFC (BA6/8) and, at an exploratory level, increased GMV in the right VLPFC (BA47) (Fig. 9). Higher GMV in right VLPFC (BA47) was observed also in adult BD-REL, in BD-I-REL and unaff-BD-REL.

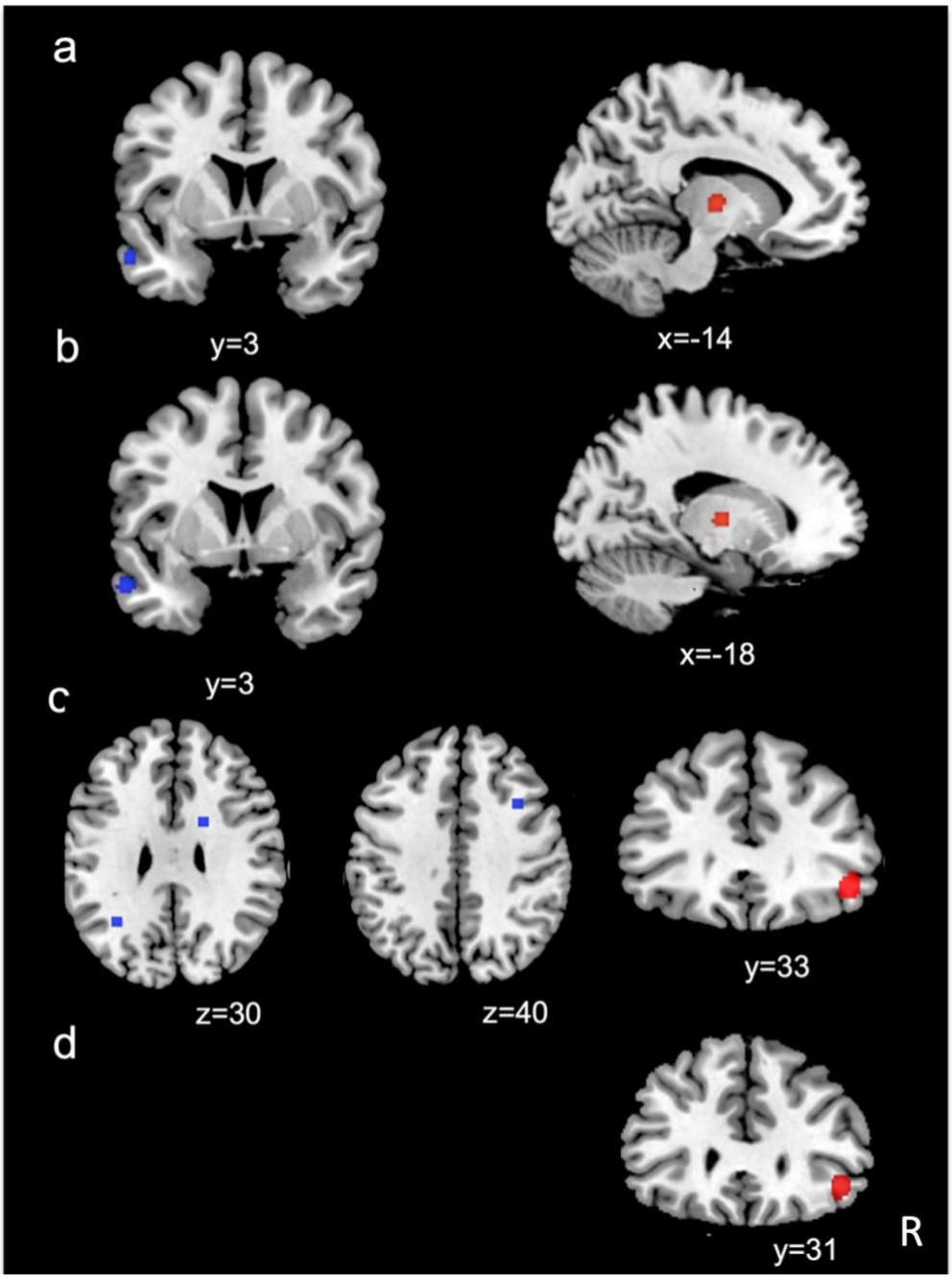

Figure 9. CBMA of structural differences in SCZ-REL compared with HC for the overall (a) and adult studies (b) and in BD-REL compared with HC for the overall (c) and adult studies (d). Increased and decreased GM in REL compared to HC are shown in red and blue, respectively. Fig. c and d represent the results of exploratory analyses. R = right.

2.3.3. Unified all-effects meta-analysis

SCZ-REL. 575 foci from fMRI and VBM studies converged in a cluster located in the right DLPFC (BA6/9) (Fig. 10).

BD-REL. 125 foci from fMRI and VBM studies converged in two cluster located in the right PHG/uncus and right VLPFC (BA 47) (Fig. 10).

BD-REL vs. SCZ-REL. BD-REL showed a higher probability of convergent fMRI and VBM alterations in the right VLPFC (BA47) compared to SCZ-REL, while SCZ-REL showed a greater likelihood of convergent alterations in fMRI and VBM studies in the right DLPFC (BA6/10) compared to BD-REL (Fig.10).

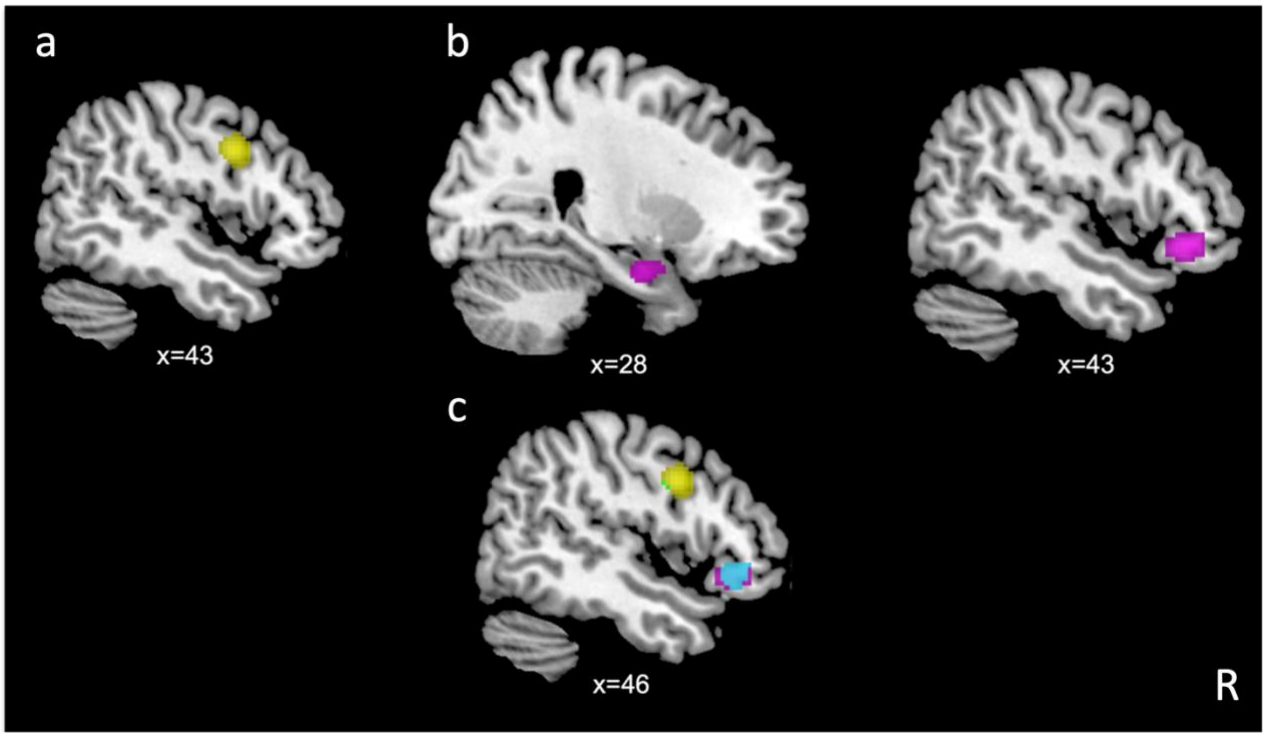

Figure 10. All-effects meta-analysis analysis of neural activity and volumetric alterations in SCZ-REL (a, yellow) and BD-REL (b, fuchsia) compared with HC. Within these clusters, voxels with greater likelihood of functional and volumetric alterations in SCZ-REL compared with BD-REL (green), and those with greater likelihood of alterations in BD-REL relative to SCZ-REL (light blue) are overlaid to (a) and (b). R = right.

2.3.4. Volume-based meta-analysis

SCZ-REL. SCZ-REL presented a smaller hippocampus (p=0.002, SMD=-0.41, 95% CI=-0.598÷-0.222-0, I^2=85.84%), thalamus (p=0.049, SMD=-0.219, 95% CI=-0.412÷-0.027, I^2=98.4%), total-GM (p=0.004, SMD=-0.186, 95% CI=-0.310÷-0.061, I^2=53.3%) and ICV (p<0.001, SMD=-0.086, 95% CI=-0.478÷-0.142, I^2=66.16%) compared to HC (Fig. 11, 12). Adult SCZ-REL showed similar results (all p's<0.05) with the exception of the thalamus. After removing the outliers (n=4), we found a reduction in striatum volume in SCZ-REL compared to HC (k=11, p=0.0011, SMD=-0.3524, 95% CI=-0.5637÷-0.1412, I^2=64.7%).

BD-REL. BD-REL showed higher ICV (p=0.025, SMD=-0.129, 95% CI=0.007÷0.252, I^2=0%) and smaller thalamus (p=0.025, SMD=-0.172, 95% CI=-0.332÷-0.022, I^2=1.98%) compared to HC (Fig. 13, 14). In adult BD-REL, amygdala was significantly smaller (p=0.03, SMD=-0.189, 95% CI=-0.361÷-0.018, I^2=22.1%) compared to age-matched HC.

BD-REL vs. SCZ-REL. The network random-effects meta-analysis showed a decrease in hippocampal volume in SCZ-REL compared to BD-REL (k=53, p=0.0052, SMD=-0.5541, 95% CI=-0.8537÷-0.2544, I^2=93.9%), which remained significant after removing outliers (k=39, p=0.0183, SMD=-0.3883, 95% CI=-0.6057÷-0.0560, I^2=60.1%).

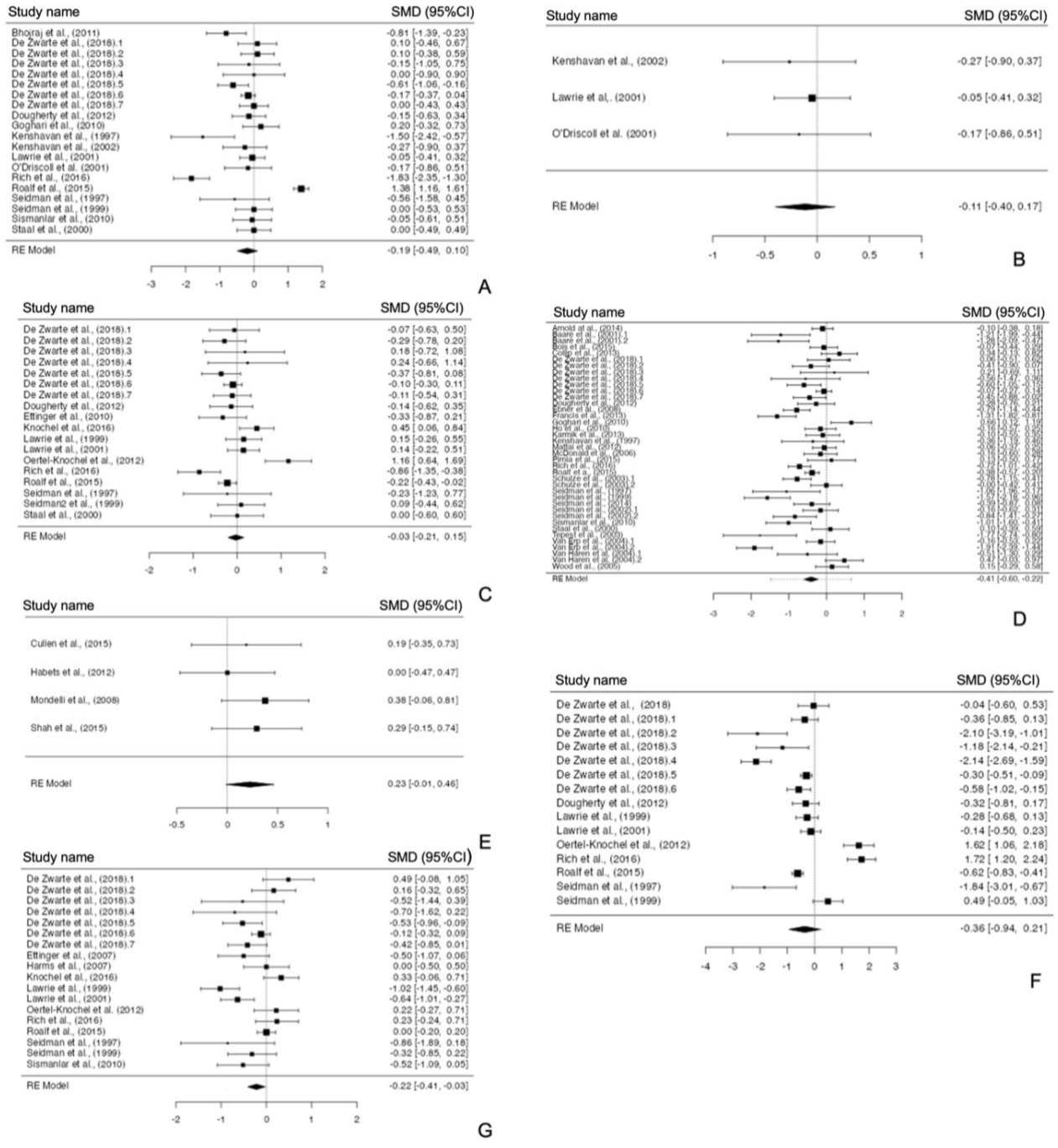

Figure 11. Forest plot showing standardized mean differences (SMD) for subcortical volumes in SCZ-REL: amygdala (A), amygdala-hippocampal complex (B), caudate (C), hippocampus (D), pituitary (E), striatum (F), thalamus (G).

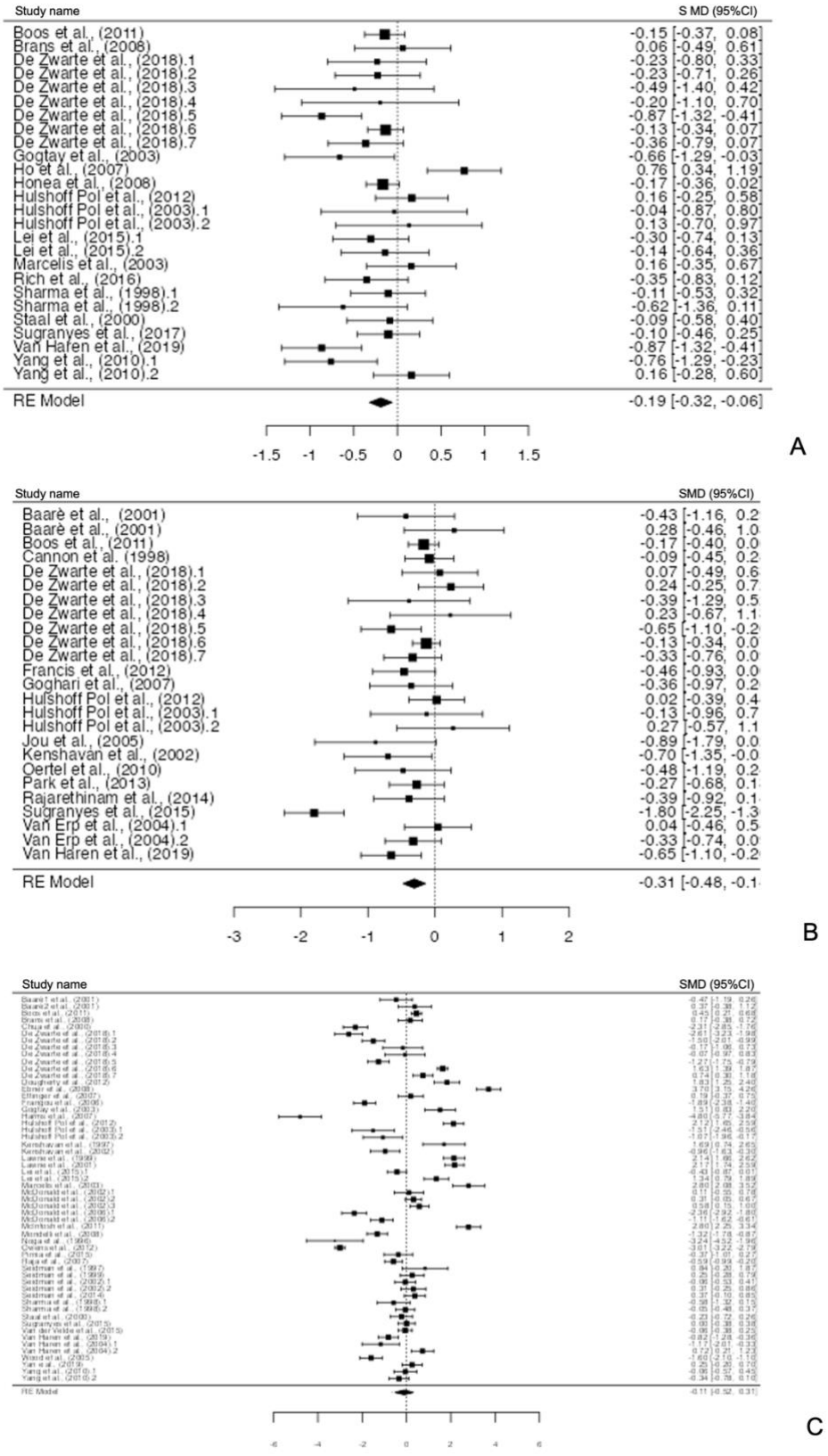

Figure 12. Forest plot showing standardized mean differences (SMD) for gray matter volume (GMV)(A), Intracranial Volume (ICV) (B), and Total Brain Volume (TBV) (C) in SCZ-REL.

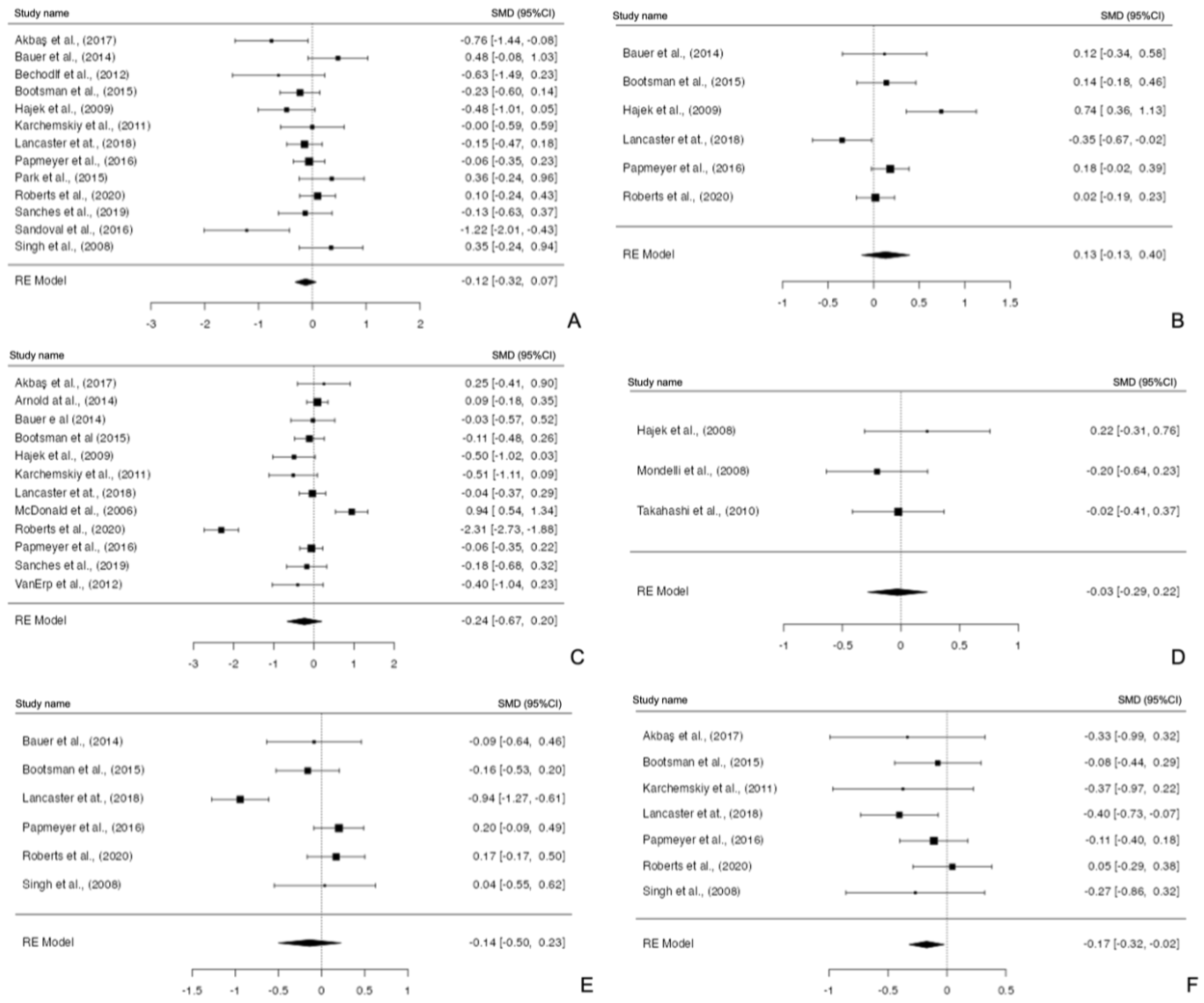

Figure 13. Forest plot showing standardized mean differences (SMD) for subcortical volumes in BD-REL: amygdala (A), caudate (B), hippocampus (C), pituitary (D), striatum (E), and thalamus (F).

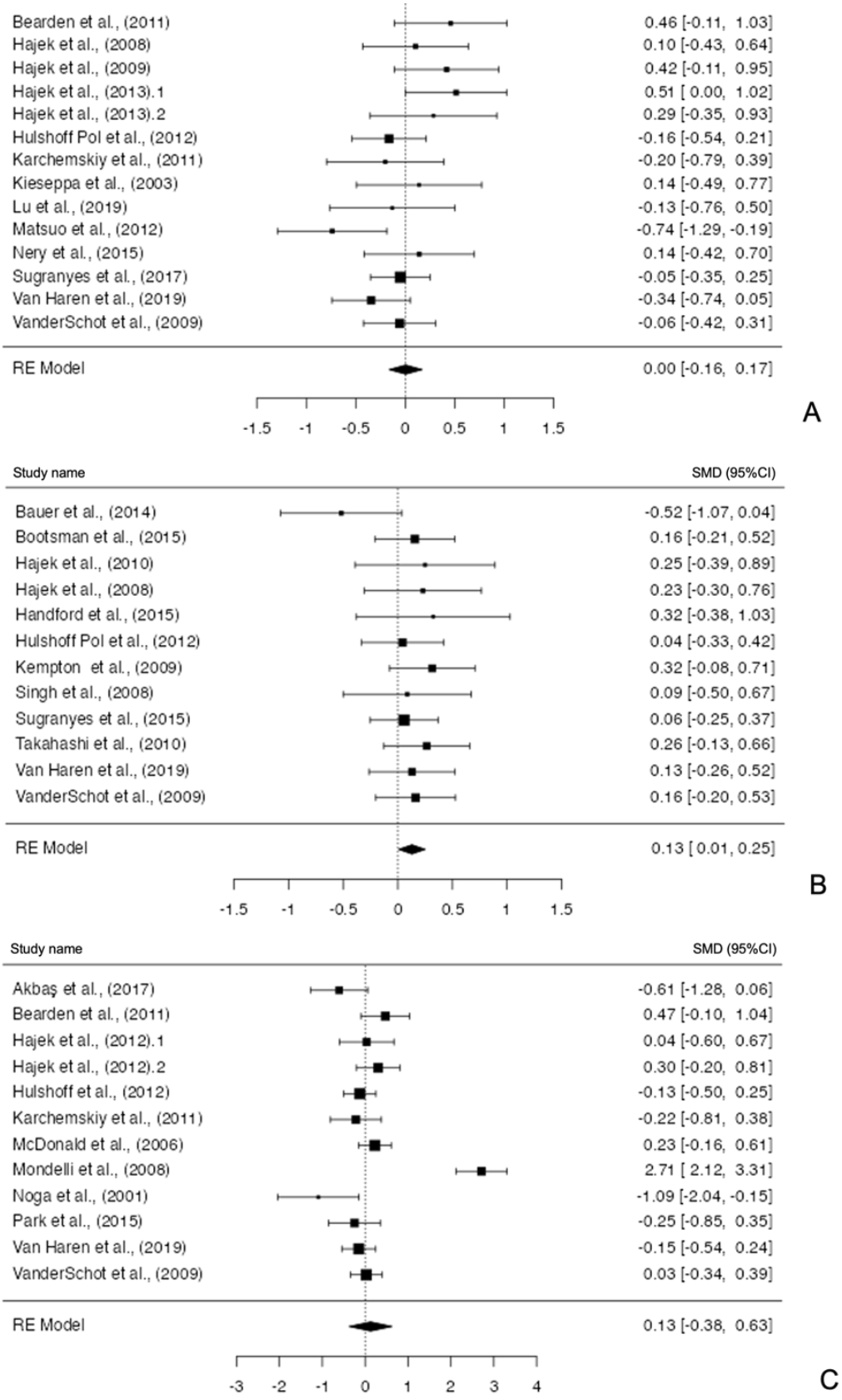

Figure 14. Forest plot showing standardized mean differences (SMD) for gray matter volume (GMV) (A), Intracranial Volume (ICV) (B), and Total Brain Volume (TBV) (C) in BD-REL.

2.4. Discussion

In our meta-analysis, we collected comprehensive multimodal evidence on brain volumetric and functional alterations in SCZ-REL and BD-REL. Current literature suggests that SCZ-REL present alterations in cortico-striatal-thalamic loop, spanning across the DLPFC and temporal regions, while BD-REL show abnormalities in thalamo-cortical and limbic regions, including VLPFC, superior parietal and medial temporal cortices. Lastly, the thalamus emerged as a common region associated with the risk for both disorders.

2.4.1. Coordinate-based meta-analysis and all-effects meta-analysis in SCZ-REL

SCZ-REL presented convergent functional and structural alterations in the right DLPFC (BA6/9). The DLPFC is implicated in higher cognitive processes, such as working memory, cognitive control, planning and response inhibition, and it plays a key role in the pathophysiology of SCZ (Becker et al., 2008; Blasi et al., 2006; Conklin et al., 2000; Smucny et al., 2021; R. Zhang et al., 2016). Interestingly, it has been shown that polygenic risk scores (PRS) for SCZ, indicating the cumulative risk for a disorder by aggregating the effects of single nucleotide polymorphisms (SNP), are associated with altered DLPFC activation during working memory paradigms, suggesting that prefrontal inefficiency can mediate the risk for SCZ (Rasetti et al., 2011; Walton et al., 2014a). Importantly, in SCZ and first-episode psychosis (FEP), prefrontal dysfunctions have been commonly described, both at rest and during the performance of cognitive tasks, mainly in the DLPFC (Callicott et al., 2003; Glahn et al., 2005; Hill et al., 2004; X. Li et al., 2019; Minzenberg et al., 2009; Molina et al., 2005; Salgado-Pineda et al., 2011; Schneider et al., 2011; Tan et al., 2005). In SCZ-REL, the DLPFC hyperactivation is considered a compensatory mechanism consisting of higher recruitment of prefrontal resources to successfully perform a cognitive task (Seidman et al., 2006). In those individuals who later develop SCZ, the prefrontal abnormalities seem to worsen with illness progression (Kani et al., 2017; Lesh et al., 2015).

Volumetric CBMA showed a decrease in volume in the superior and middle temporal regions, which is in line with mega-analyses conducted in SCZ, that showed a reduction in GM concentration and cortical thickness of the temporal gyri (Gupta et al., 2015; van Erp et al., 2018). Interestingly, previous research demonstrated that reduction in STG thickness was associated with positive symptoms in SCZ (Walton et al., 2017).

2.4.2. Volume-based meta-analysis in SCZ-REL

In line with evidence on SCZ (Konick and Friedman, 2001), we found a decrease in thalamic and hippocampal volume in SCZ-REL. Moreover, our volume-based meta-analysis showed a reduction in total GMV and ICV, consistently with a recent meta-analysis on medicated SCZ (Haijma et al., 2013a). Interestingly, after removing outlier studies, we observed a reduction in striatal volume in SCZ-REL. These results are consistent with volume changes observed in early-onset psychosis (Gurholt et al., 2020) and SCZ-REL (de Zwarte et al., 2019; Honea et al., 2008; Ivleva et al., 2013). Notably, integrated GWAS reported that genetic variants associated with SCZ were also linked with hippocampal, thalamic, striatal, GM and intracranial volumes, indicating that common genetic pathways may have regional and global effects on brain volumes (Ji et al., 2021; Smeland et al., 2018; Z. Wang et al., 2021). Overall, these results suggest that volumetric decreases in the hippocampus, thalamus, striatum, GM and ICV may be considered IP of SCZ. Additionally, we might speculate that the specific genetic variants responsible for these volumetric reductions could also be found in SCZ-REL.

2.4.3. Coordinate-based meta-analysis and unified all-effects meta-analysis in BD-REL

In BD-REL, convergent functional and structural abnormalities were observed in the right PHG/uncus and the right VLPFC (BA47). Moreover, BD-REL presented increased activation in the right PHG and VLPFC (BA13) compared to SCZ-REL. Increased limbic activation and alterations in emotional processing have been frequently described in BD during emotional tasks (C. H. Chen et al., 2011;

Townsend and Altshuler, 2012). Interestingly, a recent investigation on patients with BD and first-degree REL highlighted that REL showed a pattern of difficulties in emotion regulation, that was intermediate to the BD and HC (Van Rheenen et al., 2020). The convergent abnormalities in the PHG/uncus, as well as the limbic hyperactivation during emotive paradigms in BD-REL, confirm the findings of our previous meta-analysis (Cattarinussi et al., 2019). Taken together, these results show that REL present mild alterations in emotional processing, which may be due to limbic abnormalities. As previously reported by our research group (Cattarinussi et al., 2019), the results of the current study indicate the increased GM volume in the right VLFPC as a candidate IP of BD. Larger VLPFC volumes have also been found in first episode BD and BD, and they seem to be associated with impaired cognitive control, emotional dysregulation and impulsivity (Adler et al., 2005). Notably, BD-REL, and particularly BD-I-REL, displayed reduced parietal activation during cognitive tasks, similar to BD (Thomas et al., 2012; Townsend et al., 2010), indicating that BD-REL show functional alterations in those brain regions involved in attention, memory and social cognition (Behrmann et al., 2004; Igelström and Graziano, 2017). This is supported by the observation that BD-REL present worse cognitive abilities compared to HC (Bora and Özerdem, 2017; Calafiore et al., 2018), although conflicting results have been reported (Kjærstad et al., 2020).

2.4.4. Volume-based meta-analysis in BD-REL

The finding of lower thalamic volume, which has also been reported in BD (Hibar et al., 2016), can represent an IP of both SCZ and BD. No other differences in subcortical volumes were observed in BD-REL, consistently the results of a recent multicentric study on individuals at risk for BD (Mikolas et al., 2021). Furthermore, in line with ENIGMA studies (de Zwarte et al., 2019), we observed higher ICV in BD-REL compared to HC. In BD, no differences in ICV have been reported (Hibar et al., 2016), although some studies suggest that BD is characterized by accelerated brain aging, suggesting that disease progression might lead to a reduction in ICV.

2.4.5. Convergent and divergent abnormalities in SCZ-REL and BD-REL

Consistently with studies on SCZ and BD (Lee et al., 2020), both SCZ-REL and BD-REL showed a lower thalamic volume compared to HC, suggesting that reduced thalamic volume could represent a common neural mechanism underlying the pathogenesis of both disorders. Furthermore, alterations in the thalamo-cortical network have been frequently reported in SCZ and BD (Anticevic et al., 2014; K. Skåtun et al., 2018), highlighting the hypothesis that the thalamus might be a key area in the SCZ - BD spectrum. In line with this, our results show that genetic risk for SCZ and BD was linked with alterations in the thalamo-prefrontal circuits. Specifically, the risk for SCZ was associated with abnormalities in the DLFPC-striatal-thalamic-cortical loop, while the risk for BD was associated with alterations in the thalamo-VLPFC- circuit. In SCZ, reduced integrity of the cortico-striatal-thalamic-cortical loop seems to underlie deficits in attribution of salience, impulsive-compulsive behaviors and impaired sensorimotor functions (Fettes et al., 2017; Peters et al., 2016). Importantly, striatal alterations are a common finding in SCZ (De Rossi et al., 2016; Forns-Nadal et al., 2017; Kuo and Pogue-Geile, 2019; Okada et al., 2016), and functional and structural abnormalities in the cortico-thalamic-striatal circuits have been linked to cognitive impairments in SCZ (Sui et al., 2015). Overall, we hypothesize that abnormalities in the DLPFC, striatum and thalamus in SCZ-REL could result in alterations in cognitive processing, goal-directed behaviors and evaluation of salient information, which may evolve into positive and negative symptoms (Andersen et al., 2016). On the contrary, deficits in the thalamo-VLPFC circuit in BD-REL could result in difficultis in emotional regulation, a common feature of BD and BD-REL (Townsend and Altshuler, 2012; Van Rheenen et al., 2020). Similarly to SCZ-REL, BD-I-REL, but not the whole sample of BD-REL, showed right DLPFC hyperactivation during cognitive tasks. Although SCZ and BD are considered two distinct disorders with different clinical presentations, epidemiological and genetic studies have demonstrated a significant overlap between the genetic contributions to the disorders, and, in particular, BD-I is strongly genetically correlated with SCZ (Lichtenstein et al., 2009). In addition, increasing evidence supports the notion that neurodevelopmental changes are involved in the pathophysiology of SCZ

and BD. In SCZ, a combination of genetic and environmental factors seems to be responsible for disruptions in the neurodevelopmental trajectories, resulting in brain changes that ultimately lead to the symptoms of SCZ (Lewis and Levitt, 2002; Rapoport et al., 2005). Similarly, aberrant neurodevelopmental processes may underlie the pathophysiology of BD, and in particular early-onset BD and/or BD with psychotic symptoms (Kloiber et al., 2020). Overall, thalamo-cortical circuit alterations seem to be the result of the shared genetic mechanisms underlying both SCZ and BD, with the involvement of different prefrontal and temporal areas associated with the differential clinical phenotypes the two disorders. Furthermore, the finding of DLPFC dysfunction in SCZ-REL and BD-I-REL provides novel evidence of shared neural IP between these disorders, which may reflect a common alteration in neurodevelopmental pathways (Trevisan et al., 2022).

2.4.6. Limitations

First, we cannot exclude that some of the included REL, particularly adolescents, will develop a psychiatric disorder later in life. However, none of the SCZ-REL met the criteria for an ultra-high-risk syndrome and we also performed a meta-analysis with REL without any psychiatric symptom (i.e., anxiety, depression, conduct disorder, etc.), as well as a meta-analysis stratified by age, thus reducing the chance of inclusion of subjects at ultra-high risk to develop SCZ or BD. In addition, the MRI and fMRI studies presented significant methodological differences, including ample range of sample sizes, heterogeneous samples and different imaging acquisition and analysis pipelines. We tried to address this heterogeneity with further meta-analyses (outlier analyses and simulations).

2.5. Conclusions

This study identified a pattern of functional and structural alterations in SCZ-REL and BD-REL. Changes in cortico-striatal-thalamic networks seem to be linked to the risk for SCZ, while the risk for BD was associated with alterations in the thalamo-cortical and limbic regions. Moreover, abnormalities in the thalamus appear to be associated with the genetic risk for both SCZ and BD and

are suggestive of their role as IP for SCZ and BD. Future investigations following SCZ-REL and BD-REL longitudinally are warranted to identify the specificities in REL that develop the disorders compared to those who do not. Furthermore, the study of common neural alterations in SCZ-REL and BD-REL may expand our knowledge on the shared genetic susceptibility to these disorders, ultimately leading to the identification of IP that can help in the detection of polygenic variants associated with the vulnerability to SCZ and BD, as well as in the decomposition of psychiatric diagnoses into biologically defined illnesses.

CHAPTER 3: FIRST EPISODE PSYCHOSIS

STUDY 2: SPONTANEOUS BRAIN ACTIVITY ALTERATIONS IN FIRST-EPISODE PSYCHOSIS: A META-ANALYSIS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

3.1. Introduction

Commonly, the first manifestations of psychotic symptoms appear in late adolescence/early adulthood, dramatically impacting the individual's quality of life and functioning (Kunikata and Mino, 2003; Ortega et al., 2021). An intriguing hypothesis on the pathophysiology of psychosis suggests that psychosis may be the result of altered brain FC and spontaneous activity (Fornito et al., 2012). Spontaneous brain activity refers to neuronal activity that occurs in the absence of external stimuli (Uddin, 2020). Notably, in vitro studies on mammalian neurons have shown that neurons present ionic conductances responsible for their excitability and provide them with autorhythmic electrical oscillatory properties. Chemical or electrical contacts between the synapses of these neurons often generate synchronous firing in large groups of neurons, referred to as networks. In the networks, autorhythmic neurons may act as pacemakers or as resonators. It has been suggested that these autorhythmic properties of neurons underlie the intrinsic spontaneous functional brain activity, that is able to endow internal context to sensory input and contributes to basic functional states, including consciousness and attention (Llinás, 1988).

In the last decades, rs-fMRI has been widely used to explore spontaneous brain activity and FC in individuals with psychosis, both during the early stages of the disorder and in chronic patients (Huang et al., 2020; Y. Xu et al., 2015). In particular, rs-fMRI allows the estimation of several functional metrics of the brain, including the ALFF and the fALFF (Turner et al., 2013). Notably, one of the

pioneering resting-state studies conducted by Biswal and colleagues demonstrated that low-frequency fluctuations in the resting brain were higher in grey matter compared to white matter (Biswal et al., 1995). Later research showed that the BOLD signal correlated with local field potentials (LFP), a measure that reflects the signals generated from electrical activity in pre- and post-synaptic terminals in the brain (Khader et al., 2008; Logothetis et al., 2001; Raichle and Mintun, 2006). In particular, Logothetis and colleagues were among the first to conduct a simultaneous study of LFP and fMRI data in primates, demonstrating that LFP were correlated with BOLD signal (Logothetis et al., 2001). In recent years, the American neurologist Marcus Raichle contributed to the knowledge on the relationship between LFP and BOLD signal by showing that spontaneous fluctuations in the BOLD signal were correlated with LFP activity in the range of slow cortical potentials (Raichle, 2015). In addition, evidence from studies on brain intra- and extra-cellular calcium, potassium and chlorine concentrations, shows that the changes in ion concentration mediated by neuronal and glial activity can result in very slow spontaneous fluctuations of the BOLD signal (Krishnan et al., 2018). Moreover, important information about the correlation between spontaneous neuronal activity and low-frequency fluctuations derive from animal and human studies on the effects of anesthesia on brain activity. In particular, studies in anesthetized children have reported fMRI signal variations in primary sensory cortices due to low-frequency fluctuations at approximately 0.034 Hz, indicating that ALFF could be suggestive of regional spontaneous neuronal activity in this population (Kiviniemi et al., 2003). Similarly, fMRI investigations conducted in squirrel monkeys at different dosages of anesthetics demonstrated that increasing levels of anesthesia resulted in diminishing amplitudes of signal fluctuations and reduced power of fluctuations in the low-frequency band (Wu et al., 2016). Furthermore, several studies have demonstrated that ALFF and fALFF relate to large-scale neural synchronization and reflect physiological states of the brain (Balduzzi et al., 2008; Buzsáki and Draguhn, 2004; Yang et al., 2007).

In addition to ALFF and fALFF, local FC can be explored with ReHo, which reflects the regulation and coordination of local neuronal activity (Zang et al., 2004). Interestingly, ALFF/fALFF and ReHo present a strong positive relationship, indicating that spontaneous activity in a voxel is accompanied by an increase in synchronization with the neighboring voxels (Yuan et al., 2013; Zheng et al., 2018). The study of neural activity in subjects with FEP presents several advantages compared to chronic patients, since FEP are often drug-naïve or minimally exposed to medications (Gong et al., 2017; D. Wang et al., 2019) Moreover, FEP are only marginally affected by disease progression, which could affect neural activity (Keshavan and Schooler, 1992; Mikolas et al., 2016). Notably, several studies investigating resting-state brain activity in FEP consistently described a dysconnectivity between cortical and subcortical structures, in particular the striatum (Cui et al., 2016; Huang et al., 2020, 2018; K. H. Lee et al., 2019; X. bin Li et al., 2019; Lottman et al., 2019; Oh et al., 2020), which is consistent with the major biological hypotheses of the pathogenesis of psychosis that indicate striatal dysfunction as a core feature (Stahl, 2018). Recently, a meta-analysis of seed-based studies showed widespread resting-state FC abnormalities in FEP in several regions of the executive network (EXE), including the dorsolateral prefrontal cortex, the superior and middle frontal gyrus, the thalamus and the striatum (O'Neill et al., 2019). Another metanalysis that explored the ALFF in the cerebellum described a reduction in the subregions connected both with the motor/premotor cortex and with prefrontal cortex in drug naïve FEP (Ding et al., 2019a).

In this paper, we collected all available studies on spontaneous brain activity abnormalities in FEP using ALFF/fALFF and ReHo. On the one hand, ALFF and fALFF measure voxel-wise changes in the frequency domain, on the other ReHo is sensitive to regional variability in the time domain. Crucially, these measures are largely correlated and are complementary in measuring local spontaneous activity (An et al., 2013; Biswal et al., 2007; Deng et al., 2022; Du et al., 2022; Liu et al., 2016; Nugent et al., 2015; Shen et al., 2020; Yuan et al., 2013), present adequate test-retest reliability, as well as substantial reproducibility in the gray matter compared to global measures of brain connectivity (Holiga et al., 2018). Thus, to gain a complete understanding of the

pathophysiology of FEP, we decided to first perform a meta-analysis of ALFF/fALFF and ReHo studies separately to identify modality-specific changes; then, in accordance with previous meta-analyses (Disner et al., 2018; J. Wang et al., 2018; Yuan et al., 2022), to identify the overall changes of spontaneous neural activity, we combined these complementary measures and performed a meta-analysis of ALFF/fALFF and ReHo studies together. We hypothesized that abnormal spontaneous neural activity would be altered in large-scale brain networks, spanning prefrontal and striatal regions involved in mediating higher cognitive and affective functions.

3.2. Methods

3.2.1. Article selection and classification

In January 2022, we conducted a search on PubMed, Scopus, and Web of Science of the original papers published in peer-reviewed journals without any language restriction, following the MOOSE guidelines (Brooke et al., 2021). We used a combination of the following keywords: "Psychotic Disorders" OR "Schizophrenia" AND "first-episode" OR "first episode" AND "fMRI" OR "MRI, Functional" OR "Functional MRI" OR "Functional MRIs" OR "MRIs, Functional" AND "connectivity" OR "resting state" OR "resting-state" OR "ALFF" OR "fALFF" OR "ReHo". The reference lists of relevant reviews and meta-analyses were then checked for additional relevant studies. The initial search resulted in 802 articles. After removing duplicates and reviewing the abstracts of the remaining 488 studies articles, 53 papers were selected for full-text reading. When full-text articles were not available, direct contact was made with the authors.

We included the papers that met the following criteria: 1) original peer-reviewed papers; 2) patients met standardized diagnostic criteria (DSM, ICD) for schizophrenia spectrum psychoses (schizophrenia, schizoaffective, and schizophreniform disorders) and affective psychoses (bipolar disorder and major depression with psychotic features); 3) it was explicitly reported that patients had a duration of illness ≤5 years; 4) Talairach (TAL) or Montreal Neurological Institute (MNI) peak effect coordinates of significant differences between FEP and HC were reported. Studies were

excluded if: 1) they did not investigate spontaneous brain activity using ALFF, fALFF, or ReHo techniques; 2) they used ROI analyses; 3) peak coordinates were not available even after contacting the authors. A total of 35 studies were selected (see Fig.15).

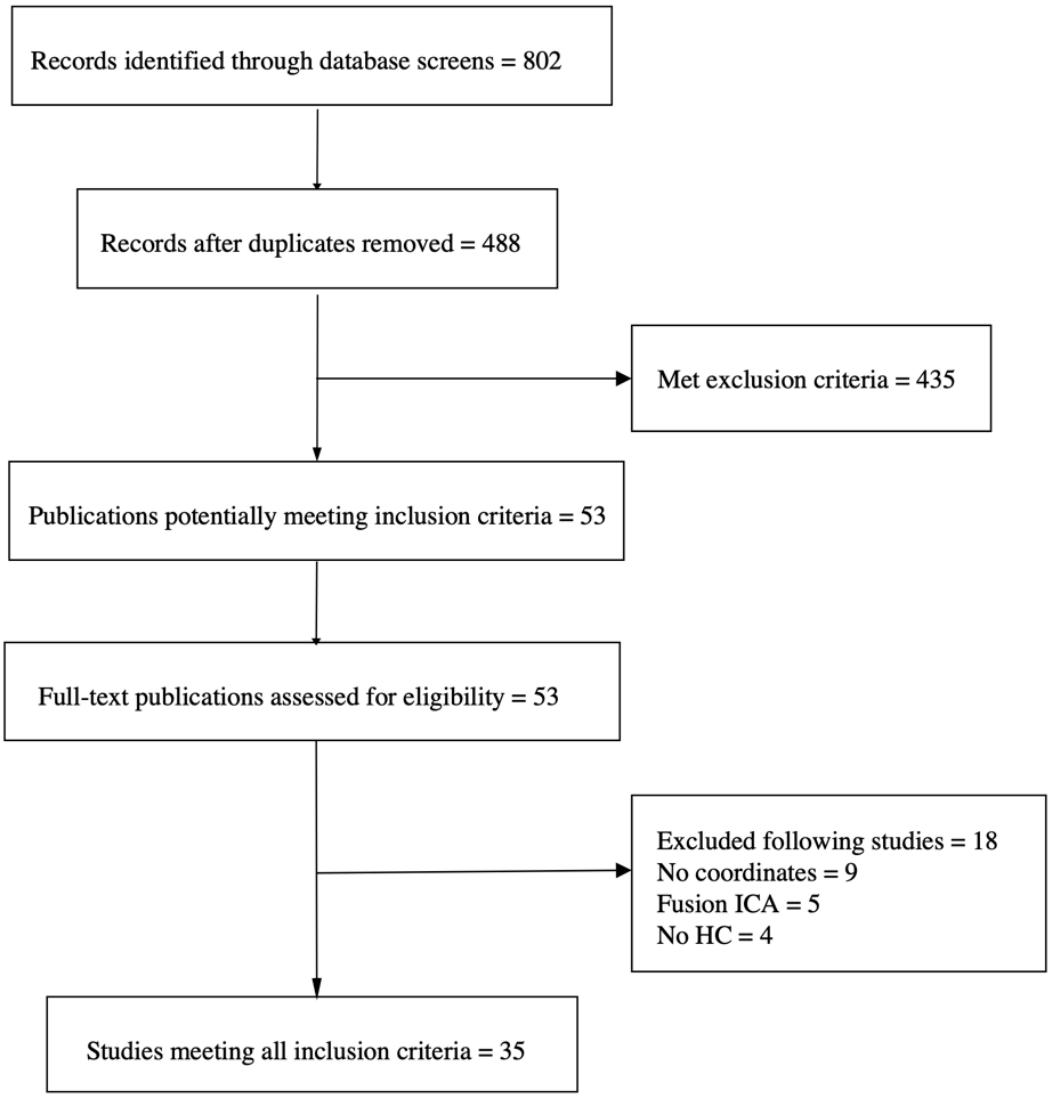

Figure 15. PRISMA flowchart for the meta-analysis of imaging articles in FEP.

Since the articles by Jiang et al. (2015) (L. Jiang et al., 2015), Cui et al. (2016) (Cui et al., 2016), Li et al. (2017) (Lin et al., 2017) and Fang et al. (2021) (Fang et al., 2021) reported data from two or more cohorts, they were treated as independent studies. Furthermore, the articles reporting multiple measures were considered as two different studies for ReHo and for ALFF/fALFF analyses (Cui et al., 2016; Fang et al., 2021; Yin et al., 2021; Zhao et al., 2018).

We also stratified the meta-analysis for age: if both samples in a study had a mean age ≤ 18 years, the population was classified as adolescent FEP, otherwise it was classified as adult FEP.

3.2.2. Quality assessment

All studies were evaluated for quality with an Imaging Methodology Quality Assessment Checklist (adapted from Strakowski et al., 2000) on the following parameters: subjects, imaging acquisition and analysis, results and conclusions (Strakowski et al., 2000).

3.2.3. Coordinate-based meta-analysis

First, we performed a CBMA for ALFF/fALFF and ReHo studies separately. Then, we conducted a global CBMA merging all rs-fMRI studies. Third, to reduce heterogeneity, we rerun global CBMA focusing on a specific age group (adult FEP ALFF/fALFF n=12, adolescent FEP ALFF/fALFF n=3; adult FEP ReHo n=10, adolescent FEP ReHo n=5). In addition, we repeated the CBMA including only those studies that explored ALFF/fALFF and ReHo in antipsychotic-naïve FEP. CBMA were computed with the revised Activation Likelihood Estimation (ALE) algorithm (Eickhoff et al., 2009; Turkeltaub et al., 2012) using GingerALE software (GingerALE 3.0.2). The coordinates of all significant peaks for each eligible contrast (FEP>HC and/or FEP<HC) were used as input for the CBMA. Analyses were performed in the Montreal Neurological Institute (MNI) reference space; when coordinated were expressed in Talairach space, they were converted to MNI (Lancaster et al., 2007). Significance was assessed using a cluster-level p(FWE)=0.05 thresholding with a cluster forming threshold of p=0.001 for n≥17 studies and a voxel-level p(FWE)=0.05 thresholding for 8≤n<17 studies, respectively (Eickhoff et al., 2016; Müller et al., 2018). To assess the effect of negative studies, we simulated the effects of including them in our meta-analyses by adding randomly created noise studies (Acar et al., 2018). The number of noise studies was equal to the number of studies that were retrieved in the initial search but were then excluded because they did not report a significant difference in ALFF/fALFF or ReHo between FEP and HC.

3.3. Results

3.3.1. Characteristics of the studies

Overall, we included 20 ALFF/fALFF (15 ALFF, 5 fALFF) and 15 ReHo studies. Of these studies, 3 ALFF and 5 ReHo studies were conducted in adolescent FEP. The mean age of FEP was 21.1 (4.7) years and 21.9 (4.5) years for HC. The mean duration of psychosis in the FEP sample was 9.41 (8.8) months. A total of 18 ALFF/fALFF investigations and 13 ReHo studies focused on drug-naïve FEP. Sociodemographic details of the participants of the included studies are reported in the Appendix.

3.3.2. Coordinate-based meta-analysis in the overall sample

ALFF/fALFF. FEP presented higher ALFF/fALFF in the right striatum compared to HC [peak coordinates (x,y,z)= 20,12,4].

ReHo. FEP presented higher ReHo in the left striatum compared to HC [peak coordinates (x,y,z)= -16,10,-4].

All measures. An increase in ALFF/fALFF and ReHo was observed in FEP compared to HC in the right striatum [peak coordinates (x,y,z)= 18,14,0], in the left striatum [peak coordinates (x,y,z)= -16,10,-2] and bilateral superior frontal gyrus/middle frontal gyrus (SFG/MFG) [peak coordinates (x,y,z)= -4,36,46], as well a decrease in the right precentral gyrus and the right inferior frontal gyrus (IFG) [peak coordinates (x,y,z)= 50,-4,30] (Fig. 16). These results did not change when only one measure per study was included in those articles reporting multiple measures for the same sample and when we included only the studies that used a correction for multiple comparisons.

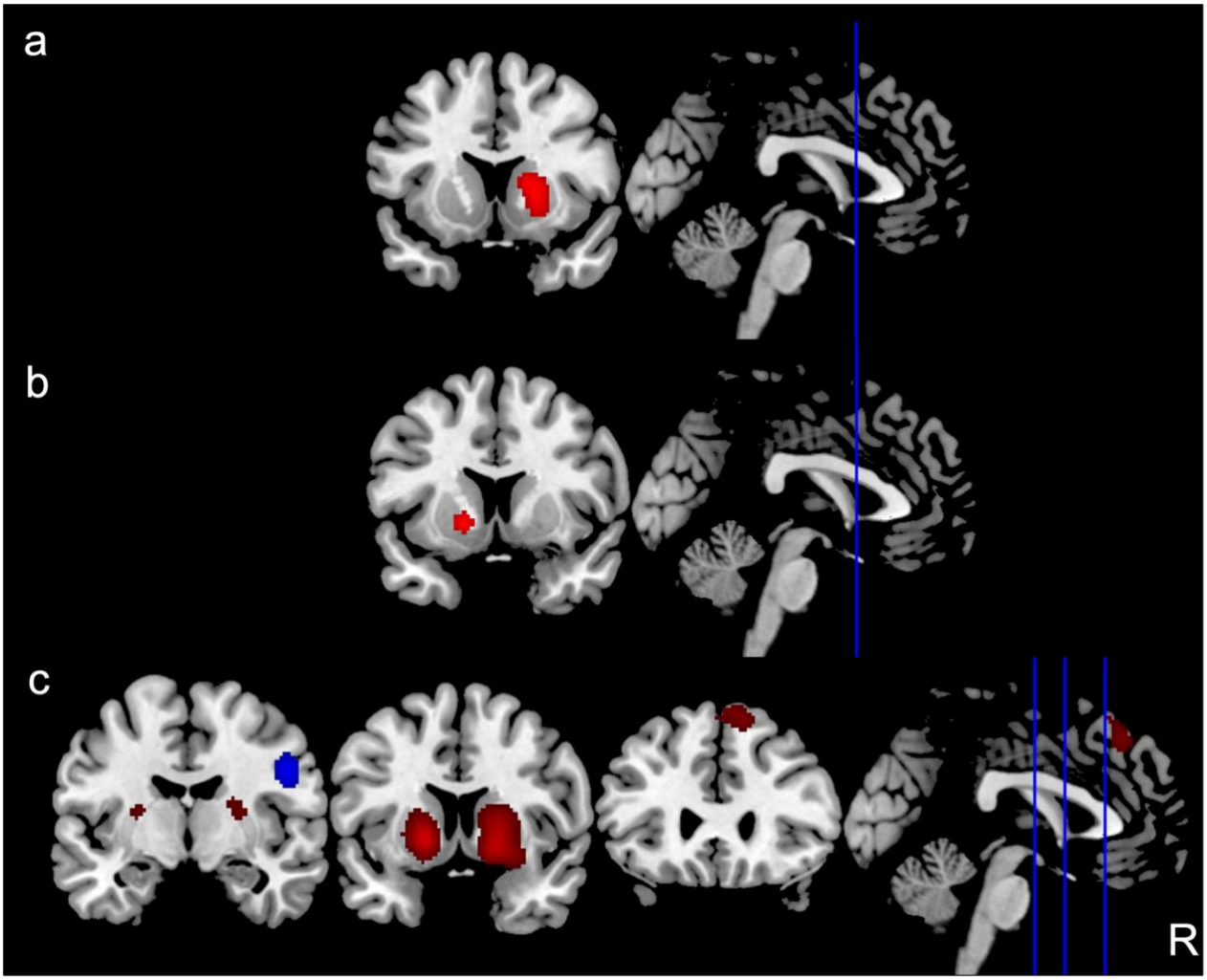

Figure 16. CBMA of intrinsic activity alterations in FEP compared to HC. Fig. a) ALFF/fALFF; Fig. b) ReHo; Fig. c) all measures**.** Increased intrinsic activity in FEP compared to HC is shown in red and blue, respectively. All images are thresholded with p<0.005, and a spatial extent of 10 voxels. R = right.

3.3.3. Coordinate-based meta-analysis in adult FEP

ALFF/fALFF. Adult FEP had higher ALFF/fALFF compared to HC in the right striatum [peak coordinates (x,y,z)= 22,12,-6].

ReHo. Adult FEP presented higher ReHo compared to HC in the left striatum [peak coordinates (x,y,z)= -16,10,-4].

All measures. An increase in ALFF/fALFF and ReHo was observed in adult FEP compared to HC in the right striatum [peak coordinates (x,y,z)= 18,14,-2], the left striatum [peak coordinates (x,y,z)= -18,12,-2) and the left SFG/MFG [peak coordinates (x,y,z)= -4,36,46], as well as a reduction in the right inferior and superior parietal lobule (IPL/SPL) [peak coordinates (x,y,z)= 46,-54,48] and in a

cluster including the left SFG, MFG, orbitofrontal gyrus and anterior cingulate (ACC) [peak coordinates (x,y,z)= -8,52,-26] (Fig. 17).

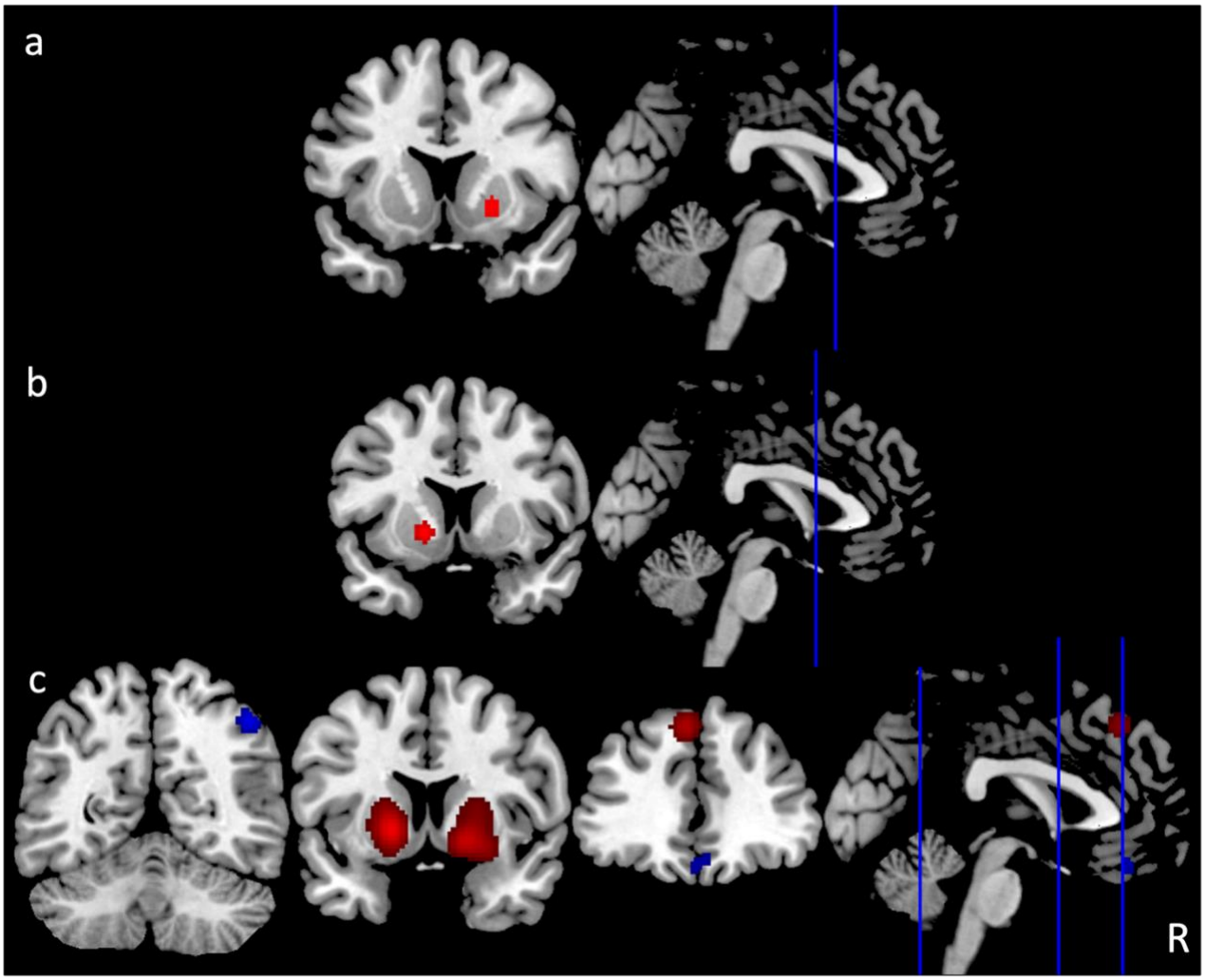

Figure 17. CBMA of intrinsic activity alterations in adult FEP compared to HC. Fig. a) ALFF/fALFF; Fig. b) ReHo; Fig. c) all measures**.** Increased intrinsic activity in adult FEP compared to HC is shown in red and blue, respectively. All images are thresholded with p<0.005, and a spatial extent of 10 voxels. R = right.

3.3.4. Coordinate-based meta-analysis in drug-naïve FEP

ALFF/fALFF. Drug-naïve FEP presented higher ALFF/fALFF compared to HC in the right striatum [peak coordinates (x,y,z)= 22,12,2].

ReHo. Drug-naïve FEP had reduced ReHo compared to HC in the right precentral gyrus and IFG [peak coordinates (x,y,z)= 50,-4,30], in the right supramarginal gyrus [peak coordinates (x,y,z)= 33,-39,42] and in the left precentral gyrus [peak coordinates (x,y,z)= -14,-24,72].

All measures. A significant increase in ALFF/fALFF and ReHo in drug-naïve FEP compared to HC was found in the right striatum [peak coordinates (x,y,z)= 18,14,-2], in the left striatum [peak coordinates (x,y,z)= -18,12,-2] and bilateral SFG/MFG [peak coordinates (x,y,z)= 12,26,58]. Moreover, we observed a decrease in ALFF/fALFF and ReHo in the right precentral gyrus and IFG [peak coordinates (x,y,z)= 50,-4,30] (Fig. 18).

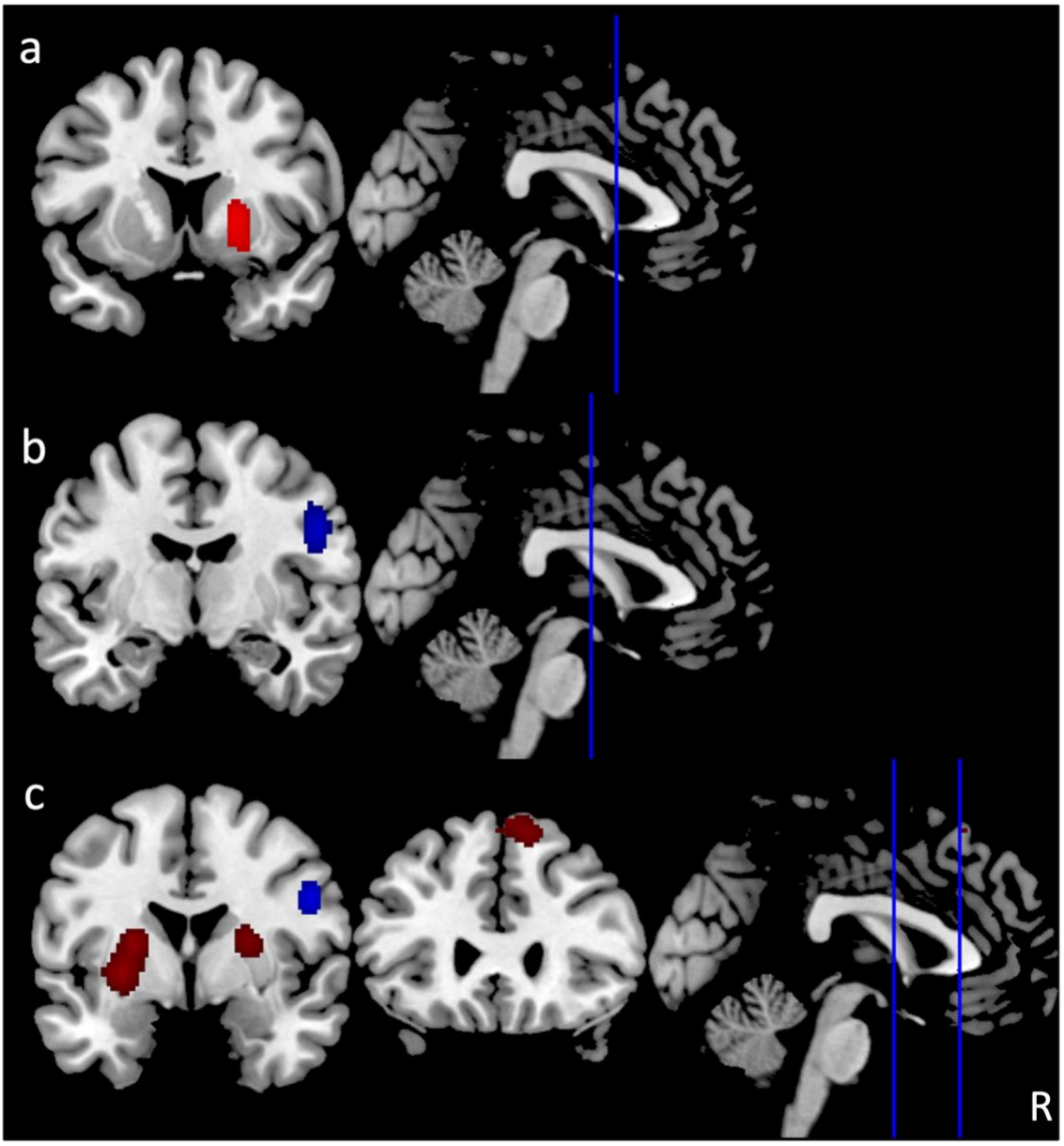

Figure 18. CBMA of intrinsic activity alterations in drug-naïve FEP compared with HC. Fig. a) ALFF/fALFF; Fig. b) ReHo; Fig. c) all measures. Increased and intrinsic activity in drug-naïve FEP compared to HC is shown in red and blue, respectively. All images are thresholded with $p<0.005$, and a spatial extent of 10 voxels. R = right.

3.4. Discussion

In this meta-analysis, we collected all available evidence on altered spontaneous brain activity in FEP measured using ALFF, fALFF and ReHo. We found higher spontaneous brain activity in the striatum, and specifically higher ALFF/fALFF in the left striatum and ReHo in the right striatum. Combining all measures spontaneous neural activity, spontaneous brain activity was increased in the bilateral striatum, bilateral SFG/MFG and decreased in the right precentral gyrus and IFG, respectively. Crucially, the results were replicated in the sample of drug-naïve patients.

3.4.1. Spontaneous brain activity alterations in FEP

The included studies consistently reported higher spontaneous activity in FEP in the bilateral striatum, a region that plays a central role in several high-order functions, including reward anticipation, cognitive and emotion processing, goal-directed behaviors, sensorimotor function and regulation of impulsivity (Bhanji and Delgado, 2014; Robbins and Everitt, 1996). In psychosis, both at early and chronic stages of the disorder, striatal abnormalities have been commonly described (Fang et al., 2021; Yin et al., 2021). In FEP, a recent investigation reported altered FC between the dorsal caudate and the primary motor cortex, as well as between the ventral rostral putamen and the right temporal occipital fusiform cortex and the dorsal rostral putamen and the ACC. Notably, these abnormalities were able to predict an improvement in negative symptoms and general functioning after one year of usual treatment (Oh et al., 2020). Additionally, a study employing independent component analysis to explore FC between brain networks revealed significant abnormalities in the caudate in FEP compared to HC (Argyelan et al., 2015). Another investigation highlighted altered ALFF in the caudate in FEP and reported that an increase in ALFF in this area could be associated with successful antipsychotic treatment (Lui et al., 2010). Increased striatal activity and local connectivity at rest can reflect an overactivity of the striatal dopamine system (Cheng et al., 2020; Howes et al., 2009). Interestingly, in our meta-analysis, the increase in spontaneous striatal activity in FEP was also

replicated in the drug-naïve sample, suggesting that resting-state activity of the striatum was not influenced by antipsychotic treatment.

In addition to striatal changes, we also found higher spontaneous activity in FEP in bilateral SFG and MFG, along with a reduction in the right precentral gyrus and IFG. Functional dysconnectivity of the fronto-striatal network plays a key role in the pathophysiology of psychosis (Howes et al., 2012; Schmitt et al., 2009; Weinberger, 1987). Indeed, alterations in the fronto-striatal circuit have been observed not only in individuals with schizophrenia (SCZ) (Meyer-Lindenberg et al., 2002) and FEP (Fornito et al., 2013), but also in individuals at genetic (Cattarinussi et al., 2022; Fornito et al., 2013) and clinical risk for psychosis (Fusar-Poli et al., 2010). Interestingly, in FEP, fronto-striatal activity appears to be affected by the duration of untreated psychosis (Manivannan et al., 2019) and it may be a biomarker for clinical improvement associated with antipsychotic treatment (Sarpal et al., 2015). Overall, our results support the notion of a fronto-striatal dysfunction in FEP that is not associated with drug treatment and may contribute to the brain dysconnectivity that has been postulated as a key the pathophysiology of psychosis.

3.4.2. Spontaneous brain activity alterations in FEP stratified by age

Adult FEP presented higher low-frequency oscillations and local connectivity in the striatum and in the SFG and MFG, similarly to what was seen in the overall sample. Additionally, adult FEP also showed lower spontaneous activity in the IPL/SPL and in a cluster that included the left SFG, MFG, orbitofrontal gyrus and ACC. Our results of altered intrinsic activity in the SFG/MFG and the SPL are consistent with findings of reduced FC in fronto-parietal regions in patients with SCZ, FEP and in individuals with at-risk mental state during tasks (Deserno et al., 2012; Schmidt et al., 2013) and rest (V. L. King et al., 2022). In addition, a seed-based study in adult FEP reported altered FC between the frontal, parietal and striatal regions, which correlated with the duration of untreated psychosis (Sarpal et al., 2017). Taken together, this evidence seems to highlight that adult FEP present resting-state alterations in the fronto-parietal-striatal circuit.

Conversely, the studies conducted in adolescents were sparse, so we cannot draw clear conclusions. Alterations in the striatum were observed also in adolescent FEP, suggesting that striatal abnormalities are present since a young age in FEP. As Weinberger first postulated, the pathophysiological changes associated with SCZ can occur during early brain development, and subsequent brain maturation might be involved in the clinical manifestations of the disorder (Weinberger, 2017). Additionally, a large body of evidence has shown that SCZ is characterized by altered plastic processes within late-maturing association cortices subserving cognitive, emotive and social functioning (Holmes et al., 2021; Lewis and González-Burgos, 2007; Sydnor et al., 2021). In line with this, the results of our CBMA in adolescent FEP suggest that brain functional alterations that can be seen as early as in the first years of adolescence could be involved in the development of the disorder, while changes in late-maturing cortices, including the prefrontal cortex (PFC), could be implicated in the clinical manifestations that appear later in life.

3.4.3. The neurotransmitter hypothesis of psychosis

Our results can also be interpreted considering the neurotransmitter hypothesis of psychosis, which suggests that SCZ is characterized by an excess of dopamine in the striatum as a consequence of increased release from the ventral tegmental area (VTA) (Weinberger, 1987). In line with this theory, numerous investigations have detected increased dopamine in the striatum in patients with SCZ (Howes et al., 2012), FEP (Schmitt et al., 2009) and in individuals at-risk for psychosis (Fusar-Poli et al., 2010). Notably, our findings of higher spontaneous activity in the bilateral striatum are in accordance with these results. Similarly, the prefrontal cortex dysfunction observed in SCZ was initially interpreted as a consequence of a reduction of dopamine levels, but several other explanations have been proposed (Simpson et al., 2010; Weinberger, 1987). Crucially, the striatum has been proposed to have an indirect effect on cortical activity via the VTA, substantia nigra and thalamus (Conn et al., 2020; Simpson et al., 2010). A reconceptualization of the dopamine hypothesis in the 1990s proposed that striatal hyperdopaminergia could be secondary to cortical hypodopaminergia

(Davis et al., 1991; Howes et al., 2015). More recently, the glutamatergic hypothesis suggested that striatal hyperdopaminergia could be secondary to cortical glutamate alterations. In particular, it has been suggested that neurodevelopmental abnormalities could cause a hypofunction of NMDA receptors (NMDAR) in cortical GABAergic parvalbumin-positive interneurons (Gonzalez-Burgos and Lewis, 2012). Consequently, the glutamate release from a cortico-cortical pyramidal neuron is unable to efficiently stimulate the GABAergic neurons, which in turn fail to inhibit downstream cortico-brainstem pyramidal neurons, leading to excessive release of glutamate in VTA and dopamine in the striatum (Howes et al., 2015). Glutamatergic excess has been frequently reported in SCZ, in particular in the medial PFC and striatum, and seems to be specific to the early stages of the disorder (Dempster et al., 2020; Egerton et al., 2018). Consistently, elevated glutamate concentrations in the ACC were found to be inversely correlated with striatal dopamine synthesis in FEP (Jauhar et al., 2018).

Notably, our results showed a different lateralization of ALFF/fALFF and ReHo alterations, with higher ALFF/fALFF in FEP relative to HC in the right striatum and higher ReHo in the left striatum. Positron emission tomography studies have reported an asymmetry in cerebral dopamine neurotransmission, both in healthy individuals (Martin-Soelch et al., 2011; Tomer et al., 2013) and in antipsychotic-naïve SCZ patients (Hietala et al., 1999). Therefore, our findings suggest that ALFF/fALFF and ReHo, which are distinct albeit complementary measures, could be differentially sensitive to dopamine neurotransmission, thus reflecting the underlying the lateralization of the dopamine system.

3.4.4. Limitations

First, the fMRI studies presented significant methodological differences, including diagnostic criteria for FEP and heterogenous imaging acquisition and analysis pipelines. Second, some of the patients were not treatment-naïve and therefore previous drug treatments may have affected their neural activity. For this reason, we stratified our analyses by treatment and confirmed the main findings.

Lastly, some studies presented a limited sample size, which could have led to publication or outcome reporting biases.

3.5. Conclusions

Our study provides robust evidence for spontaneous neural activity alterations in FEP, involving in particular the fronto-striatal circuit. The discovery of fronto-striatal dysconnectivity in early psychosis is consistent with the notion that this alteration represents a core neural deficit of the illness. Future longitudinal studies aimed at identifying the prognostic meaning of changes in spontaneous neural activity will be important to predict the progression of FEP to full-blown psychiatric disorders to carry out personalized preventive treatments.

4. STUDY 3: CORRELATIONS BETWEEN ALTERATIONS IN RESTING-STATE FUNCTIONAL CONNECTIVITY AND PSYCHOPATHOLOGICAL FEATURES IN FIRST-EPISODE PSYCHOSIS

4.1. Introduction

Despite decades of research have helped us gain insight into the pathophysiology of psychosis, the underlying neurobiology of psychotic symptoms remains still largely unclear (Heckers, 2011; H. Huang et al., 2020). Against a long-standing tradition that tried to explain psychosis focusing on single brain areas, the dysconnectivity hypothesis claims a primary etiological role for abnormal functional integration between different brain regions (K. Friston et al., 2016; K. J. Friston and Frith, 1995). The functional integration can be characterized in terms of FC, defined as the temporal dependence between remote areas (K. J. Friston, 2011; van den Heuvel & Hulshoff Pol, 2010). Rs-fMRI has been widely used to assess spontaneous brain activity and the FC in the human brain, revealing the presence of networks of anatomically separated regions that are strongly functionally linked during rest (van den Heuvel & Hulshoff Pol, 2010). Moreover, it allowed us to assess the weaker temporal relationships among these networks, defined as FNC (Jafri et al., 2008).

In chronic psychosis, along with subcortico-cortical dysconnectivity (Ramsay, 2019), meta-analytic evidence suggests hypoconnectivity within networks, including the default mode network (DMN), salience network (SAL), somatosensory network (SM) and executive network (EXE) (Dong et al., 2018; S. Li et al., 2019). Notably, the chronic effects of antipsychotic treatment are believed to influence the brain structure and function in patients with psychosis, along with other factors related to the disease, such as metabolic changes, chronic stress, smoking, and substance abuse (DeLisi, 2008; Jonas et al., 2022). Moreover, well-established evidence shows that the disease process itself can contribute to progressive cognitive decline and brain changes from the earliest stages (DeLisi, 2008). Therefore, the assessment of FEP, where the influence of these processes is limited, could play

a pivotal role in elucidating the genuine neurobiology of the disease (Gong et al., 2017; H. Huang et al., 2020). Evidence supporting altered FC in FEP is heterogeneous, although some consistent findings have been reported, such as the hypoconnectivity between the striatum and the cortical structures of the SN, including the anterior insula and the cingulate cortex (H. Huang et al., 2020; X. bin Li et al., 2019). Moreover, Sarpal et al. (2015) observed an increase of FC between the cingulate cortex and the striatum with clinical improvement of the psychosis in FEP (Sarpal et al., 2015). Notably, the functional dysconnectivity of the striatum and of other SN structures has been also linked to impaired cognitive performance in psychosis (Sheffield & Barch, 2016).

Growing evidence reveals that the brain displays spontaneous fluctuations of activity and FC on a slow time scale, while most available studies measured the FC averaged over multiple minutes (the so-called static FC), blending different states and possibly accounting for the heterogeneity of the results (Damaraju et al., 2014; Fu et al., 2021). In contrast, dynamic FC (dFC) analyses allow the study of evolving FC patterns, in terms of the characteristics and persistence of reoccurring states and quantitative measures of the dynamism of FC patterns over time (Long et al., 2021; Miller et al., 2016a), dFC changes seem to correspond to electrophysiological properties and to predict cognitive functioning in healthy adults (Allen et al., 2018; Cabral et al., 2017). In addition, dFC have been reported in many neurological and psychiatric disorders (Fiorenzato et al., 2019; J. Wang et al., 2020; C. Zhao et al., 2022). In psychosis, dFC analyses revealed alterations that occur only during certain dynamic states and thus unobservable with static FC (Damaraju et al., 2014), reduced dynamism (Miller et al., 2016a; Rabany et al., 2019) and a tendency to reduce dwell time in strongly connected states and increase it in sparsely connected states (Cattarinussi et al., 2023a; Damaraju et al., 2014; Fu et al., 2021; Rabany et al., 2019). Notably, a contrasting pattern of reduced dwelling in sparsely connected states was shown in unmedicated patients (Lottman et al., 2017a). Importantly, literature on dFC alterations in FEP is still limited (Zhang et al., 2021; L. Zhao et al., 2022), resulting in a gap of knowledge about the changes over time of FC patterns in this populations.

In this study, we employed rs-fMRI to explore static and dynamic connectivity in a sample of FEP patients, with an onset within the past five years prior to the study. We hypothesized that the application of dynamic FC analysis on a sample of patients minimally affected by characteristic progressive brain changes would provide significant insight into the neurobiological underpinnings of psychosis, revealing early changes that may go undetected in the static FC analysis, thus hypothesizing the predominance of strongly connected states, in accordance to the finding of Lottman et al. (2017) on unmedicated patients (Lottman et al., 2017a), and reduced dynamic fluidity. Furthermore, we evaluated the relationship between FC metrics and a range of clinical, cognitive, and emotional variables. We hypothesized that a reduction in dynamic fluidity would be associated with an increase in psychotic symptoms and that static and dynamic parameters have an influence on psychotic symptoms and cognition.

4.2. Material and methods

4.2.1. Participants

Data were obtained from the online database Human Connectome Project for Early Psychosis Release 1.1 (https://www.humanconnectome.org/study/human-connectome-project-for-early-psychosis). In short, the study contains neuroimaging, psychopathological, and cognitive data of 183 outpatients with the diagnosis of schizophrenia spectrum disorders, major depressive disorder (MDD) with psychotic features or BD with psychotic features with symptoms onset within five years prior to study entry, and 68 matched HC. The inclusion criteria for both groups were: a) 16 to 35 years of age; b) ability to provide informed consent; c) ability to communicate in English. Exclusion criteria were: a) active medical condition affecting the brain or cognitive functioning; b) mental retardation; c) contraindications to MRI; d) substance-induced psychosis or psychotic disorder due to a medical condition; e) severe substance use disorder in the previous 90 days; f) ECT treatment in the previous 12 months; h) high suicide risk. HC had no lifetime or current BD, recurrent MDD, SCZ, and other psychotic disorders, current anxiety disorder, no first-degree family member diagnosed with SCZ

spectrum disorders, and no psychiatric medications at the time of study entry. Additionally, we excluded subjects with current alcohol (n=6) or cannabis abuse (n=16). 2 subjects were also excluded for not having completed the diagnostic interview. Of the remaining participants, subjects were excluded from the analysis due to the lack of structural imaging data (n=3) and excessive head movement during the rs-fMRI scan (n = 6), which resulted in a final sample of 96 patients with FEP and 56 HC.

4.2.2. Clinical assessment and cognitive measures

Diagnostic clinical interviews were conducted with the Structural Clinical Interview for DSM-5 – Research Version (SCID-5-RV) (First et al., 2015), Intellectual abilities were assessed with the WASI-II (McCrimmon & Smith, 2013; Wechsler, 2011), cognitive functions with the NIH Toolbox Cognition (Denboer et al., 2014; Hodes et al., 2013; Weintraub et al., 2014), psychotic symptoms with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

4.2.3. Imaging acquisition

Images were acquired at three imaging sites (Brigham and Women's Hospital, McLean Hospital, and Indiana University) with three Siemens MAGNETOM Prisma 3T scanners. Two sites employed a 32-channel head coil, and the other used a 64-channel head and neck coil, with the neck channels turned off. All protocols were based on the 2016 CCF template protocol (https://www.humanconnectome.org/hcp-protocols-ccf-template). Briefly, the protocol scan sequences were as follows: T1-weighted MPRAGE structural scans of 0.8mm isotropic resolution (TR=2400ms; TE=2.24ms; flip angle=8). and rs-fMRI of 2 mm isotropic resolution, multiband acceleration factor of 8, TR/TE= 720/37 ms, FOV=208 mm; 72 slices; Flip angle= 52°; time points=400 acquired with AP phase encoding. Subjects were asked to remain still during the scans. During the rs-fMRI subjects remained with their eyes open and were required to fixate a white cross on a dark background, to think of nothing in particular, and not to fall asleep.

4.2.4. Image processing

Structural and functional magnetic resonance imaging data were preprocessed using Data Processing & Analysis for Brain Imaging (DPABI) and Statistical Parametrical Mapping 12 (SPM12), running under MATLAB R2016a (The Mathworks, Sherborn, MA, USA). Briefly, all images were reoriented and realigned for head motion correction. Then, the T1-weighted images were segmented into grey matter, white matter, and cerebrospinal fluid. Grey matter images were then normalized to the MNI space using DARTEL registration with a resulting isotropic voxel size of 3 mm x 3 mm x 3 mm. A group spatial ICA was carried out using GIFT (http://icatb.sourceforge.net) to extract independent components, consisting of spatial maps and TCs and to evaluate FNC. A total of 53 ICs were identified by applying the Neuromark algorithm, belonging to subcortical (SC), auditory (AUD), SM, visual (VIS), EXE, DMN and cerebellum (CB) networks (Du et al., 2020). Spatial maps were thresholded with a t-score > mean + 4 standard deviations(Allen et al., 2014). The multitaper method was used to estimate spectra from detrended TCs using Chronux (http://chronux.org). Detrended TCs after despiking and low-pass filtering (cut-off = 0.15 Hz) were pairwise correlated, and Fisher's Z-transformed, thus resulting in a 53 x 53 FNC cross-correlation matrix.

4.2.5. Static functional network connectivity

First, for each feature type, we created a design matrix with the following predictors: age, diagnosis (FEP, HC), mean frame-wise displacement, and root mean square of motion (Power et al., 2012; van Dijk et al., 2012). Then, we used a backward step-wise multivariate selection approach within GIFT 3.0 toolbox (http://mialab.mrn.org/software/mancovan/index.html) to determine differences in SMs, spectra, and FNC between FEP and HC. We first conducted a multivariate analysis of covariance to identify significant predictors (false discovery rate (FDR) (Genovese et al., 2002) with α=0.05) within the design matrix and then used univariate analysis to test the significance of the reduced model relative to the full model to identify specific relationships between diagnosis and spatial maps,

spectra, and FNC for each intrinsic network, while ruling out the effects of covariates. All coordinates are reported in MNI space.

4.2.6. Dynamic functional connectivity

The dFC analysis was conducted with a sliding window approach using the dFNC toolbox within GIFT 3.0 (Damaraju et al., 2014). To estimate dFC, we used two different statistical approaches. The first, clustering state analysis, assesses the structure of reoccurring patterns as well as the frequency and duration of their presentation. To identify these cluster states in the native state space, k-means clustering (k=5) was repeated 100 times on windowed FC matrices. Then, the mean time dwelled in each state by each subject was estimated. The number of transitions (NT) between clusters during the scan provides an estimate of dynamism, although possibly underestimating it when multiple FC pattern changes occur within a single cluster and overestimating it when multiple minimal pattern changes occur between different clusters (Allen et al., 2014; Miller et al., 2016a). The second approach, meta-states analysis, can overcome this problem (Miller et al., 2016a). Each dFC matrix is modeled as a weighted sum of a finite number of maximally independent states, obtained using spatial group ICA on group dFC with a model order of 5, which is considered an adequate dimensionality to include complex additive effects and keeps a richly featured basis pattern (Miller et al., 2016a). The resulting vectors, called meta-states, are used for the characterization of moving from one meta-state to another in a 5-dimensional space. The trajectories from one meta-state to another within this space are calculated for each subject at any time point. Here, the dynamism is reflected by measures of dynamic fluidity, including the number of meta-states and of meta-state changes, and measures of dynamic range, which include the span, i.e., the largest city block distance between two meta-states, and the total distance of the meta-states, i.e., the overall distance traveled through the 5-dimensional space.

4.2.7. Statistical analyses

For clinical, demographic, cognitive, and imaging measures, we estimated differences between groups using a t-test, χ^2, or Mann-Whitney test, as appropriate. Given our *a priori* hypothesis of reduced dynamism in psychosis (Mennigen et al., 2018; Miller et al., 2016a; Rabany et al., 2019), partial correlations were used to assess the correlation between the meta-state parameters and positive symptoms, which are the hallmarks of psychotic disorders. Additional exploratory partial correlation analyses were performed in FEP to assess the relationship between clinical and cognitive scores and all parameters of static FC and dFC, applying an FWE correction at p=0.05 for multiple comparisons. In these correlations, for those variables that were not normally distributed in the FEP group ($p<0.05$ on the Shapiro-Wilk test), we used Box-Cox transformations. Chlorpromazine equivalents, estimated with the Gardner approach,(Gardner et al., 2010) were included as nuisance variables in all correlation analyses to exclude the role of antipsychotic treatment in the relationship. Furthermore, between-group differences and brain behavior correlations were assessed in antipsychotic-free subjects. All statistical analyses were performed with Jamovi 2.3.21.0 (The jamovi, 2022) and with R version 4.2.2 (R Core Team, 2022).

4.3. Results

4.3.1. Demographic, clinical and cognitive data

The sample included 96 FEP (mean age=22.8 ± 3.9 years, 58 males) and 56 HC (mean age=24.8 ± 4.2 years, 37 males). No differences in sex (χ^2=0.48, p=0.49) were observed between the two groups, while age (U=1896, p=0.002) and IQ (Welch's t=-5.4, $p<0.001$) were significantly lower in FEP compared to HC. Sociodemographic and clinical data are reported in the Appendix. Patients with FEP performed significantly lower on the NIH Toolbox Cognition (U=1020, $p<0.001$), with a mean score of 100 ± 13.5 in FEP and of 113 ± 8.09 in HC. In the FEP group, 44 patients (45.8%) were taking antipsychotics and 52 (54.2%) were antipsychotics-free.

4.3.2. Static Functional Network Connectivity

Multivariate analyses yielded significant differences in spatial maps between FEP and HC. In particular, we found an effect of the diagnosis on the spatial maps of the SC (IC1, IC4) AUD (IC 7), SM (IC8-13, IC15-16), VIS (IC17-21, IC23, IC24), EXE (IC26, IC32), DMN (IC47, IC48) and CB (IC51) networks. Within the SC network, univariate analyses confirmed that the IC loadings were significantly increased in the left caudate/putamen (x,y,z=-12,9,-3; IC4) and right putamen (x,y,z=18,9,-3; IC4) and decreased in the right globus pallidus (x,y,z=21,0,-6; IC4) in FEP compared to HC; within the SM network, the IC loadings were significantly increased in the left (x,y,z=-48,-30,9; IC8) and right superior temporal gyrus (STG) (x,y,z=48,-15,9; IC8), left superior frontal gyrus (SFG) (x,y,z =-24,-3,66; IC16), left inferior parietal lobule (IPL) (x,y,z=-54,-30,39; IC16) and right postcentral gyrus (x,y,z=56,-27,45; IC16), and reduced in the right SFG (x,y,z=18,-12,69; IC10, left postcentral gyrus (x,y,z=-51,-24,-51; IC11), right precentral gyrus (x,y,z=45,-21,51; IC11) and right precuneus (x,y,z=9,-69,54; IC15). Lastly, within the VIS network, the IC loadings were reduced in the left superior occipital gyrus (SOG) (x,y,z=-12,-100,11; IC18) and the right precuneus (x,y,z=15,-63,21; IC17; Fig. 19). The analyses on antipsychotic-free subjects confirmed all the results of medicated FEP.

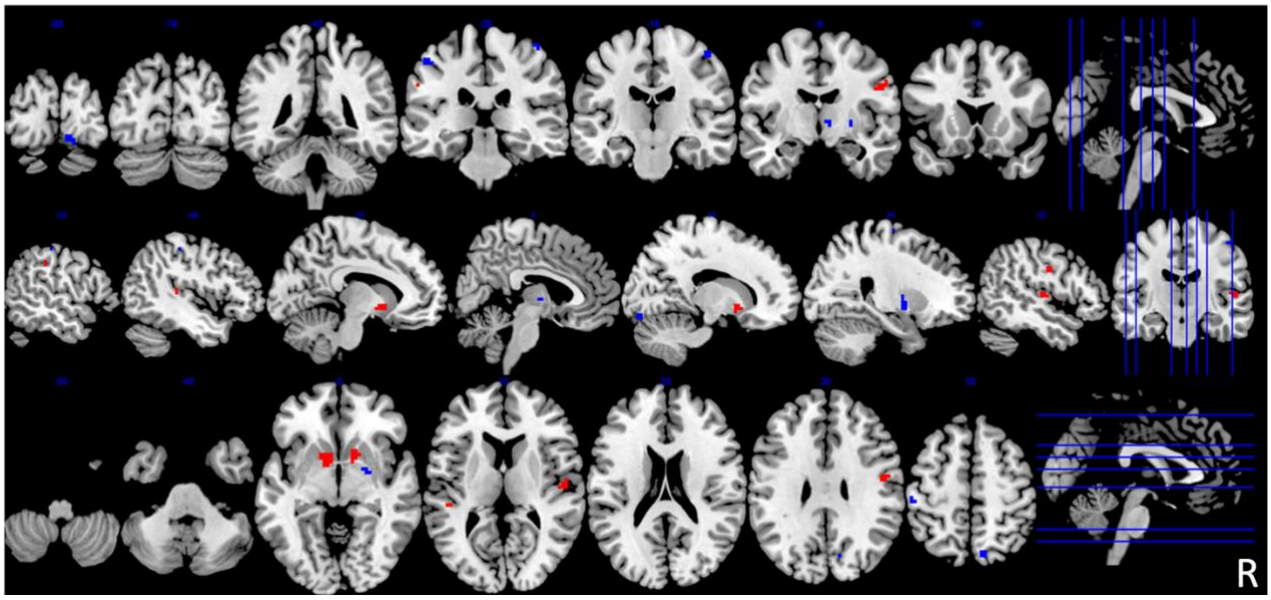

Figure 19. Intrinsic connectivity in FEP compared to HC in the left and right striatum within the SC network, left and right superior temporal gyrus, left superior frontal gyrus, left inferior parietal lobule and right postcentral gyrus within the SM network. Decreased connectivity in FEP compared to HC in the right striatum within the SC network, in the right SFG, left postcentral gyrus, right precentral gyrus and right precuneus within the SM network, in the right precuneus and left superior occipital gyrus within the VIS network. Increased connectivity in FEP compared to HC is shown in red and blue, respectively. All images are thresholded with $p<0.005$, and a spatial extent of 10 voxels. R = right.

4.3.3. Dynamic Functional Network Connectivity

Among the five estimated cluster states, State 1 was characterized by the strongest correlation pattern, followed for correlation magnitude by State 3 and 4, which showed comparable strength, by State 2, and eventually by State 5 (Fig. 20). Two sample t-tests showed dFC differences between FEP and HC in two states ($\alpha<0.05$): in State 4, FEP had an increased negative coupling between the EXE (IC26) and AUD (IC7); in State 5, characterized by the weakest correlation pattern, FEP displayed reduced positive coupling within the SC (IC2 and IC4), reduced negative coupling between the SC (IC5) and the SM (IC8, IC9, and IC11), reduced positive coupling within the SM (IC8 and IC16) and reduced positive the SM (IC15) and the CB (IC51). The cluster state analyses revealed that FEP presented a longer dwelling in State 1 ($U=1208$, $p<0.001$), State 2 ($U=139$, $p<0.001$) and State 3 ($U=2020$, $p=0.011$), and reduced dwelling in State 4 ($U=1173$, $p<0.001$) and State 5 ($U=210$, $p<0.001$) compared to HC. Moreover, FEP presented a higher NT ($U=2079$, $p=0.02$) (Fig. 21a). Meta-states analysis showed reduced state span ($U=1488$, $p<0.001$), number of states ($t=-5.2$, $p<0.001$),

number of state changes (t=-4.8, p<0.001) and total distance (t=-4.58, p<0.001) (Fig. 21b). The analyses on antipsychotic-free subjects confirm all the results.

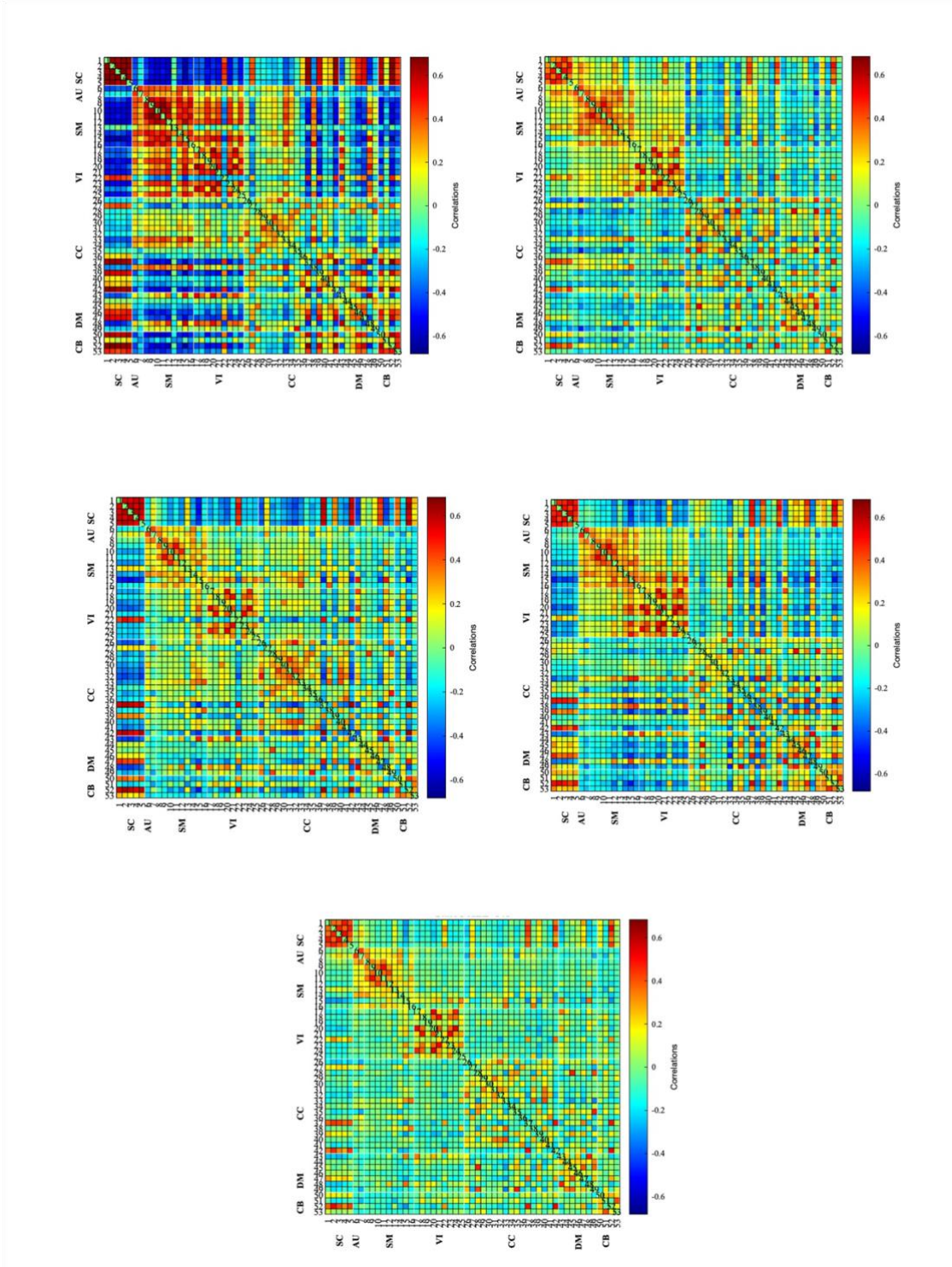

Figure 20. Cluster states resulting from the dFC analysis were identified by k-means clustering on the whole-group level. Median cluster centroids in the correlation matrices for each of the five dFC States are reported. The color bar indicates the magnitude of each correlation. SC, subcortical network; AU, auditory network; SM, sensorimotor network; VI, visual network; CC, cognitive control network; DM default mode network; CB, cerebellum network.

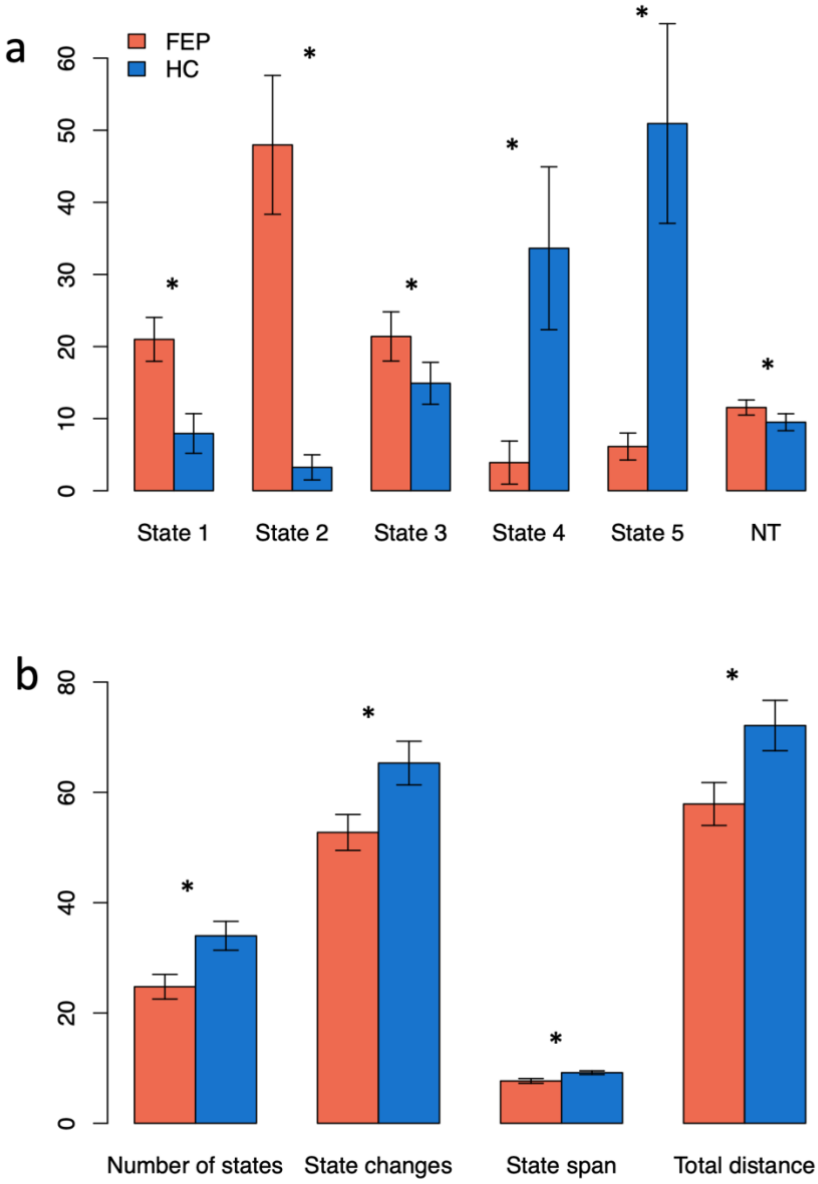

Figure 21. Fig. a) Dwell times in the different state clusters and number of transitions between clusters in FEP and HC with respective confidence intervals. FEP is indicated in gray and HC in white. Dwell times are given in number of TR windows. All the differences are significant at $p < .05$. NT, Number of transitions. Fig. b) Number of meta-states, number of state changes, state span, and total distance, with respective confidence intervals. All the differences are significant at $p < .05$.

4.3.4. Association between static and dynamic connectivity and clinical and cognitive variables

In FEP, within the SC, the static FC of the right putamen (IC4) was negatively correlated with the NIH-T cognitive composite score (r=-0.326, p=0.002, p_{FWE}=0.009) (Fig. 22). Exploratory correlation analyses between static FC and psychopathology and cognition showed that, within the SM, the static FC of the left postcentral gyrus (IC16) and of the right SFG (IC10) was positively correlated with the PANSS positive score (rho=0.250, p=0.016 and rho=0.225, p=0.030), and the static FC of the left

SFG (IC16) was positively correlated with the NIH-T cognitive composite score (rho=0.216, p=0.049); within the SC, the static FC of the right putamen (IC4) was positively correlated with the PANSS general score (r=0.216, p=0.042).

As for dynamic connectivity, in the FEP, PANSS positive score was negatively and significantly correlated with the number of meta-state changes and the total distance (rho=-0.218, p=0.036 and rho=-0.209, p=0.044, Fig. 23) and marginally with the absolute number of meta-states (rho=-0.198, p=0.058).

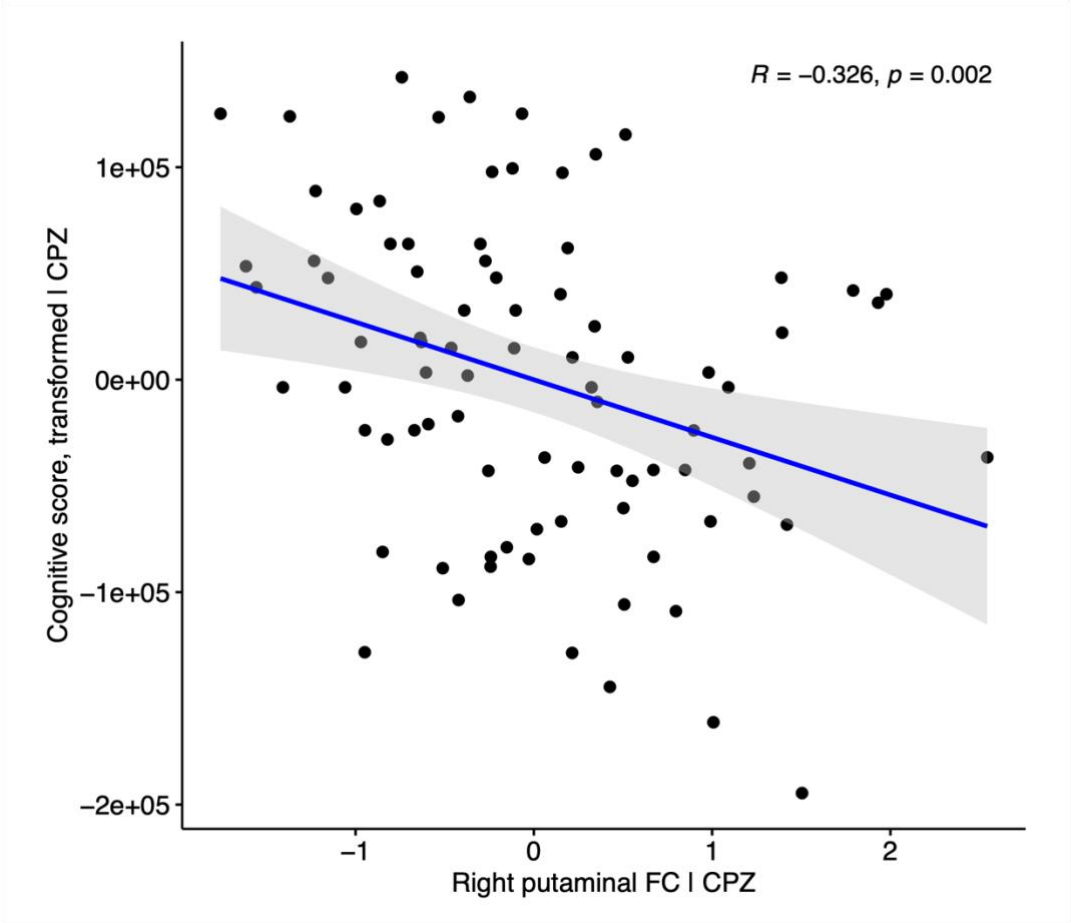

Figure 22. Scatterplot of the partial correlation between the NIHT-cognitive composite score, boxcox transformed and the static FC of the right striatum within SC, adjusted for chlorpromazine equivalents. FC, functional connectivity; CPZ, chlorpromazine equivalents.

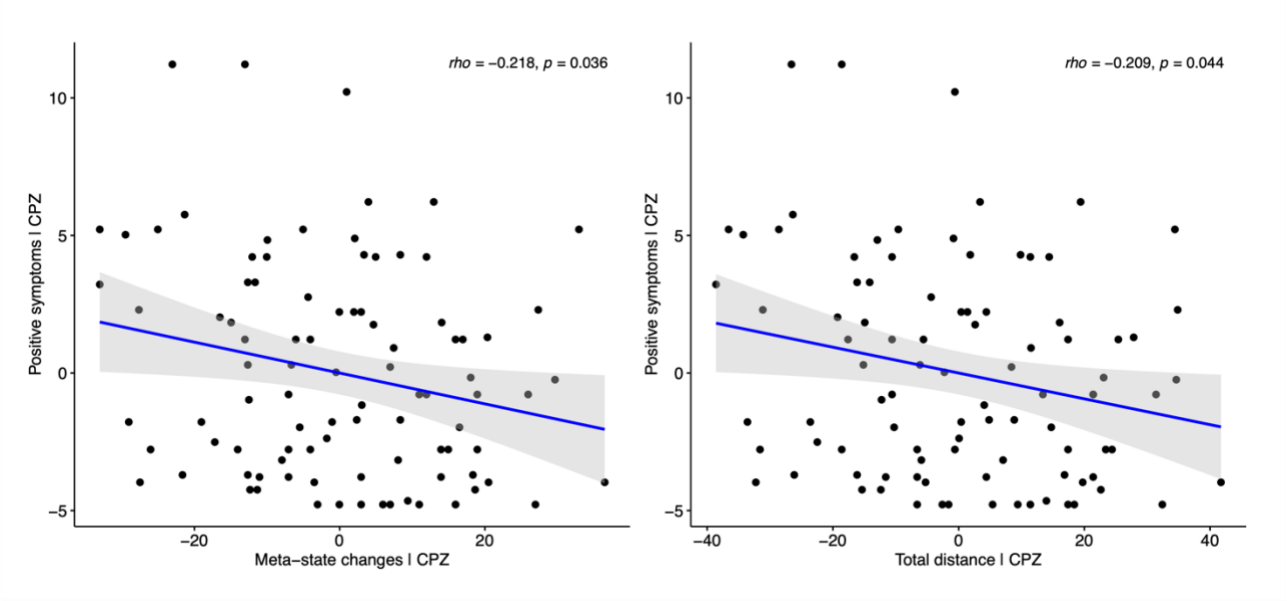

Figure 22. Scatterplots of partial correlations between PANSS positive scores and FC dynamism, adjusted for chlorpromazine equivalents. CPZ, chlorpromazine equivalents.

4.4. Discussion

The overarching objective of this study was to explore the dynamics of the neural network in a sample of FEP and to examine the association between FC metrics and clinical and cognitive features. Three main findings emerged: a) FEP showed altered static FC in cortical and subcortical regions of the SC, SM, and VIS networks; b) FEP had reduced meta-state parameters, including the number of states, state changes, state span, and total distance of the meta-states compared to HC, as well as increased NT, longer dwell time in states characterized by high within-network correlation in SC and high anti-correlation between SC and the other networks, and shorter dwell time in the less connected state; c) in FEP, increased static FC of the right putamen within the SC network was associated with worse cognition and dynamism was correlated with greater positive symptoms.

4.4.1. Static Functional Network Connectivity

Compared to HC, FEP showed an increase and a decrease in static FC in the striatum within the SC network. The striatum has been implicated in numerous high-order functions, including cognitive and emotion processing, goal-directed behaviors (Robbins & Everitt, 1996), reward anticipation (Bhanji &

Delgado, 2014) and regulation of impulsivity (Tschernegg et al., 2015). Abnormalities in the ventral and dorsal striatum have been consistently reported in psychosis, regardless of disease stage, and also in individuals at genetic risk for the disorder (Cattarinussi et al., 2022). In particular, functional neuroimaging studies have described abnormal striatal coupling with default mode and cognitive control networks in SCZ (Brakowski et al., 2022) and significant FC alterations within the caudate nucleus in FEP compared to HC (Argyelan et al., 2015). Moreover, recent meta-analytic evidence has shown that patients with FEP present altered intrinsic neural activity in the striatum, and this was true also in antipsychotic-naïve individuals (Cattarinussi et al., 2023b). The altered synchronization that we observed may be an effect of the increased mesostriatal dopaminergic firing, known to play a fundamental role in the pathogenesis of psychosis (McCutcheon et al., 2019) and could be in relation to the dysconnectivity between striatum and other brain regions, that is a consistent finding in studies in FEP (Huang et al., 2018, 2020; Lee et al., 2019; X. bin Li et al., 2019; Lottman et al., 2019; Oh et al., 2020). Notably, altered static FC of the striatum was correlated with cognitive function. This result corroborates previous studies that showed an association between structural and functional striatal alterations in SCZ and working memory deficits (Huang et al., 2019), abnormal attention processes (Simpson et al., 2010) and, furthermore, with negative symptoms (Brandl et al., 2022; Kirschner et al., 2016). Several lines of research have suggested that, in psychosis, abnormalities in the subcortical DA system can affect the striatum, possibly resulting in cognitive deficits (see below) (Conn et al., 2020; McCutcheon et al., 2019).

In addition, we also observed abnormalities in several regions of the SM network, including fronto-temporo-parietal areas, which is in line with the idea of psychomotor mechanisms in psychiatric disorders (Northoff et al., 2021). Interestingly, alterations in the striatal and SM networks have also been demonstrated in first-episode drug-naïve SCZ patients, suggesting that altered dopaminergic function in the striatum might lead to abnormal FC within the subcortical-cortical circuitry (Martino et al., 2018). Notably, these authors also observed a correlation between thalamo-sensorimotor FC and psychopathological symptoms measured with the PANSS (Martino et al., 2018). Interestingly,

our findings also corroborate a recent meta-analysis in schizophrenia that showed altered interconnections between the striatum and sensorimotor regions, including the lateral prefrontal cortex and pre-supplementary motor area (Chase et al., 2018). Taken together, this evidence suggests that striatal and SM systems are complexly linked, and their interplay might be involved in the pathophysiology of psychotic disorders.

Lastly, FEP presented a decreased static FC in the right precuneus and in the left SOG within the VIS network. Dysfunction in visual perception and in the visual system have long been associated with psychosis (Butler et al., 2008; Butler & Javitt, 2005; Tibber et al., 2013). In particular, alterations in VIS network FC have been reported both during task and at rest in SCZ, and these seem to be correlated with task-switching costs and with hallucination severity (Li et al., 2020). In FEP, a magnetoencephalography study demonstrated dysconnectivity across the VIS network in response to increasing cognitive demands, which was associated with positive symptoms (Sklar et al., 2022). Interestingly, psychosis appears to be characterized by an aberrant peripheral visual signal, to which the thalamus and frontal cortex could first fail to adapt, followed by the lower visual processing areas (Adámek et al., 2022). This mechanism be the basis of dysconnectivity within the VIS, along with perceptual and cognitive alterations (Adámek et al., 2022).

4.4.2. Dynamic Functional Connectivity

Our results showed that all of the dFC parameters were altered in FEP, including cluster states and metastates. In general, FEP had more occurrences of states 1 and 3, characterized by the strongest high within-network correlation in SC. Thus, the overall hyperconnectivity that we found within the SC network in static FC analyses might be linked to the longer time dwelled in these states. State 1 also presents the strongest anti-correlation between SC and AU, SM and VIS. Similarly, state 3 is characterized by strong anti-correlation between SC and the same networks.

Previous studies in FEP found a decrease in static FC between the striatum and several cortical areas related to auditory, sensorimotor and visual functions (Cui et al., 2016; H. Huang et al., 2018; Lin et

al., 2018). Differently, other studies reported an anteroposterior pattern with positive correlations in more frontal regions and negative correlations in more posterior regions (Fornito et al., 2013; Sarpal et al., 2015). These results could reflect the effects of cortical dysfunction affecting dopaminergic or glutamatergic neurotransmission on striatal activity in psychosis or a striatal indirect efference on cortical areas mediated by VTA, substantia nigra and thalamus (Conn et al., 2020; Dandash et al., 2017; Simpson et al., 2010).

In line with prior research, the dFC analysis revealed many FC alterations that were undetected by the static FC analysis, probably due to their time-varying occurrence. In FEP, in the weakly connected state 5, the SM showed reduced negative coupling with the SC, in line with a previous finding of their hyperconnectivity in a sparsely connected state in psychotic patients (Lottman et al., 2017a), while reduced positive coupling with the CB and between its components. These alterations could contribute to explaining the presence of sensorimotor abnormalities described in treatment-naïve psychosis (Hirjak et al., 2015; Martino et al., 2020). In FEP, the meta-state analysis showed a reduced number of states and lower total distance, which are consistent with earlier findings of reduced number of states, transitions and limited state variability in SCZ (Rabany et al., 2019). Moreover, we found that FEP had reduced state span and state changes. The NT was increased in FEP relative to HC. Previous evidence has shown an association between the NT and PANSS scores, suggesting a relationship between dFC and symptom severity (Rabany et al., 2019). This may suggest that patients with FEP tend to have more frequent transitions between a limited number of states with frequent engagement and disengagement of networks with altered connectivity and this may probably be due to the instability deriving from the altered dopamine signaling, which is known to affect FC (Caravaggio et al., 2022; Honey, 2003). Moreover, reduced dynamic fluidity and increased persistence in states with disrupted FC in FEP can indicate a reduced temporal coordination between brain networks implicated in affect, motor function, and behavior (Northoff et al., 2021). These changes may be reflected by an overall impairment of the dynamics of the brain, not only at the level of specific states, where FEP tend to dwell more in states with increased network interplay, but also

at a global level with reduced overall dynamics of the brain, as previously shown in SCZ and BD (Cattarinussi et al., 2023a; Miller et al., 2016b).

Consistently with our hypothesis and with the previous finding by Rabany et al. (2019) (Rabany et al., 2019), abnormalities in dynamic fluidity and range were associated with positive symptoms. Notably, this association was not driven by age or antipsychotic treatment. Notably, our findings in FEP are in partial contrast with the findings of Miller et al. (2016) in chronic SCZ, in which hallucinations were negatively correlated with dynamic fluidity, while delusions were weakly positively correlated (Miller et al., 2016a). We speculate that the latter results might be due to the confounding effects of the chronicity of the disorder and the treatment, and lifestyle changes that characterize patients with SCZ and support the rationale of investigating dysconnectivity in FEP.

4.4.3. Dopamine alterations and functional dysconnectivity

Dopamine dysregulation has a central role in psychosis' neurobiology, and multiple evidence links it to the rising of both cognitive and positive symptoms (Howes & Kapur, 2009), as well as to FC aberrancies (Kim et al., 2019; Sabaroedin et al., 2023), although the specific mechanisms are still unknown. The dopamine levels are known to have an inverted U-shaped relationship with cognitive functions, such as working memory and cognitive control (Bertolino et al., 2009; Cools & D'Esposito, 2011), while the relationship with brain activity and FC appears to be more complex (Cools & D'Esposito, 2011; Tian et al., 2013; Xu et al., 2016). For instance, Tian et al. (2013) found that the estimated dopamine levels had an inverted U-shaped relationship with the FC of the PFC, while an upright U-shaped relationship with the FC of the striatum (Tian et al., 2013). Hypothetically, the striatal FC increase that we observed can follow from increased striatal dopamine signaling, which could result in cognitive deficits via altered cortico-striato-thalamic circuits (Conn et al., 2020; Simpson et al., 2010).

Dopamine levels could also impact the dFC, as suggested by the effect of antidopaminergic treatments on the time dwelled in different dynamic states (Lottman et al., 2017b; Y. Wang et al., 2021).

Moreover, dopamine activity, which is characterized by a complex balance of tonic and phasic bursts (Grace, 1991), could influence the dynamic fluidity and range. Interestingly, a major hypothesis on psychosis is that the steady-state tonic bursts are reduced, determining an increase of dopamine, thus increasing the phasic bursts, produced by external stimuli, and leading to symptoms (Grace, 1991).

4.4.4. Limitations

Some methodological aspects limit the generalizability of our results. First, our patients were not antipsychotic-naïve, and, although to a lesser extent than patients with chronic exposition, their FC could be influenced by medications. Nonetheless, we used statistical correction for this nuisance variable and repeated our analyses in a drug-free sample, and confirmed our main findings. Second, although psychosis could be conceptualized as a syndrome associated with different illnesses, combining data from non-affective and affective disorders could have hidden some differences in the biology of psychosis in these distinct disorders (Baker et al., 2014). Nonetheless, we wanted to study alterations of brain connectivity that were shared across disorders and underlie a common construct of psychosis. Third, an important limitation of our dynamic FC approach could be that the clustering is applied to all the participants together so that the estimated states are not specific for FEP patients or HC but averaged across the whole group, just as Huang et al. (2020) noticed for group-ICA (Huang et al., 2018). Although the application of dynamic FC separately for each group increases specificity, results cannot be compared between groups as the combination of networks in states will differ across groups.

4.6. Conclusions

In conclusion, by using static and dynamic FC analyses focusing on the changes of the brain network configurations over time, we provided further evidence of dysconnectivity in FEP. In particular, we observed static hyperconnectivity of the bilateral striatum in the SC network, converging with the dopaminergic hypothesis of psychosis. Additionally, we displayed lower dynamism in FEP compared

to HC, suggesting a reduced temporal coordination between brain networks implicated in affect, motor function, and behavior. Moreover, in FEP, we detected a negative correlation between fluid and crystallized cognitive functions and the static FC of the right striatum and a negative correlation between positive symptoms and dynamism. If replicated, these results may inform future research to design neural intervention strategies targeted at developing novel effective treatments.

5. STUDY 4: PERIPHERAL INFLAMMATION AND SPONTENEOUS BRAIN ACTIVITY IN FIRST EPISODE PSYCHOSIS

5.1. Introduction

Systemic inflammation has been identified as a potential risk factor in the pathophysiology of several psychiatric disorders (Mondelli et al., 2015), including MDD (Beurel et al., 2020), BD (Muneer, 2016) and SCZ (Müller, 2018). In particular for SCZ, the vulnerability-stress model first proposed over half a century ago (Meehl, 1962) has been recently expanded to become the vulnerability-stress-inflammation model. According to this theory, a mental or physical stress might result in an increase in systemic inflammation, that can in turn trigger SCZ in vulnerable individuals (Müller, 2018). Crucially, evidence from animal and human studies has consistently reported alterations in inflammatory processes in SCZ, spanning from increased C-reactive protein (CRP), dysregulation of cytokines, elevated neutrophils and autoantibodies levels and microglia alterations (Ermakov et al., 2022; Laskaris et al., 2016; Momtazmanesh et al., 2019). Based on this assumption, several trials have been conducted to examine the potential therapeutic effects in SCZ of drugs with anti-inflammatory properties. Among these, the Benefit of Minocycline on negative symptoms of schizophrenia (BeneMin) study, a randomized, placebo-controlled, multicentric trial of 12-month minocycline, has given clear negative results (Deakin et al., 2018). However, the potential effects of minocycline, which may vary across individuals, may not be detected in coarse phenotypes such as clinical symptoms, even if present at the level of the brain.

Over the last two decades, MRI research has investigated the effects of systemic inflammation in the brain, and an increasing plethora of studies exploring brain structural and functional changes associated to inflammation in affective disorders is now available (Frodl and Amico, 2014). In SCZ, recent structural studies have reported an association between inflammatory markers and alterations in subcortical volumes and cortical thickness (Hoang et al., 2022), ventricular volume (Chen et al.,

2023) and white matter metrics (Serpa et al., 2023). Furthermore, two fMRI studies by the same research group explored task-based connectivity of the DMN in association with childhood traumas and reported that higher levels of interleukin-6 (IL-6) mediate the association between higher childhood neglect and increased DMN connectivity (King et al., 2023; S. King et al., 2022). In addition to task-based studies, inflammation seems to influence also resting-state fMRI parameters, as reported by investigations in MDD (Beckmann et al., 2022; Kitzbichler et al., 2021). Rs-fMRI has been widely used to explore intrinsic spontaneous brain activity and FC, describing differences at the regional level and in large-scale networks (Huang et al., 2020a; Y. Xu et al., 2015a). In particular, it allows the estimation of several functional metrics of the brain, including ALFF, fALFF and ReHo. To our knowledge, no studies so far have investigated the effect of systemic inflammation on resting-state fMRI parameters in SCZ. Therefore, to gain ad deeper understanding of how inflammation impacts spontaneous brain activity and local connectivity at rest and contribute to symptom severity, we analyzed resting-state fMRI data acquired from patients with FEP and different levels of inflammation using ALFF, fALFF and ReHo techniques. Crucially, the study of the interplay between immune parameters and neuroimaging alterations in FEP patients might provide a deeper understanding of the immunological and functional brain mechanisms associated with the pathophysiology of the disorder, as these are not influenced by the chronic exposure to antipsychotics medications (Caruso et al., 2020; Ceresoli-Borroni et al., 2006). Consistent with studies showing that higher levels of plasma CRP predicted increased concentrations of inflammatory cytokines in both plasma and cerebrospinal fluid in patients with MDD (Felger et al., 2020), plasma concentrations of CRP were used to determine the effects of inflammation on resting-state brain activity and local connectivity. Based on previous literature that identified levels of CRP $\geq$ 3 mg/L as indicative of low-grade inflammation (Lombardo et al., 2022; Nettis et al., 2021; Osimo et al., 2019; Pearson et al., 2003), individuals were stratified according to their serum levels CRP into CRP < 3 mg/L and CRP $\geq$ 3 mg/L.

Based on evidence in MDD revealing decreased FC between subcortical structures and ventral medial (vm) PFC in association with inflammation (Felger et al., 2016; Mehta et al., 2018), we hypothesized that the hub region for inflammation would be identified in ventral regions of mPFC, and that this ventral hub would exhibit decreased FC with extensively distributed cortical and limbic regions as a function of increasing CRP. Furthermore, since murine studies have demonstrated brain penetration of minocycline in prefrontal and limbic regions, suggesting the propensity of minocycline to produce an anti-inflammatory effect in these regions, we hypothesized that minocycline could reduce the functional alterations associated to inflammation in these areas.

5.2. Method

5.2.1. Study design and intervention

The data of this study were collected from the benefit of minocycline on negative symptoms of schizophrenia (BeneMin) trial. The full protocol and primary outcomes have been published elsewhere (Deakin et al., 2018; Lisiecka et al., 2015). Briefly, between April 2013 and March 2015 subjects with a diagnosis of first episode of schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV) were enrolled in eight UK centers. Inclusion criteria were: a) subjects aged between 16 and 40 years; b) subjects within five years of symptoms onset; c) score greater than two for one or more items (P1 delusions, P2 conceptual disorganization, P3 hallucinatory behavior, or P6 suspiciousness) of the PANSS (Kay et al., 1987) indicating positive symptomatology; d) ability to give written informed consent and e) fluency in English. Participants were excluded if they were at severe risk of suicide or violence or had a current diagnosis of substance use disorder. Ethical approval was granted by the Northwest Greater Manchester Central UK NHS Research Ethics Committee (reference number 11/NW/0218). In addition to their current treatment, participants were randomly assigned to minocycline (100 mg capsules twice daily for two weeks and then increased to 300 mg daily for the remainder of the twelve-month study period) or matching placebo. A total of 207 participants were recruited and followed-up at two months, six months, nine months, and 12

months from baseline. See Appendix for the participants flow through the trial. Blood samples to test for high-sensitivity C-reactive protein (hs-CRP) and cytokines were collected at baseline and repeated at months six, nice, and 12 months. MRI scans were performed at baseline and repeated at 12 months. In the current study, we included the following data: age, gender, IQ, BMI, PANSS scores, auditory verbal learning test (AVLT) scores, circulating serum cytokines and MRI data collected at baseline and 12 month-follow-up.

5.2.2. Inflammatory markers analysis

Peripheral blood samples were processed as previously described (Krynicki et al., 2021). In addition to hs-CRP, the following cytokines were measured: interleukin (IL)-1RA, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, Tumor Necrosis Factor-alfa (TNF-alfa), and Interferon-gamma (IFN-gamma). Cytokine levels were normalized through logarithmic transformation. Serum levels of IL-1 and IL-4 levels were undetectable, therefore IL-1 and IL-4 were excluded from our analyses.

5.2.3. Neuroimaging analysis

MRI sequences were based on the NeuroPsyGrid multi-center validation and reliability study (Suckling et al., 2012). T1-weighted high-resolution MRI magnetization-prepared rapid gradient-echo (MPRAGE/SPGR) and proton density and T2-weighted dual echo (PD/T2) were acquired. In addition, T2-weighted gradient echo planar imaging (EPI) during resting state were acquired to investigate spontaneous brain activity.

Functional and structural MRI data were pre-processed with DPABI and SPM12, running under the MATLAB R2022a (The Mathworks, Sherborn, MA, USA). First, individual images were visually inspected for anatomical abnormalities and artefacts. Then, images were reoriented into AC-PC space and realigned for head motion correction. After this, T1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid. Images were then normalized to the Montreal

Neurological Institute (MNI) standard brain using DARTEL registration with a resulting isotropic voxel size of 3x3x3 mm^3.

5.2.4. Spontaneous brain activity and local connectivity

We explored ALFF, fALFF and ReHo using DPABI. For ALFF analyses, the filtered time series of each voxel was transformed into the frequency domain with a Fast Fourier Transform and the power spectrum was obtained. ALFF were measured calculating the square root of the signal across 0.01–0.08 Hz for each voxel (Zang et al., 2007). For standardization purposes and to reduce the influence of individual variation in ALFF values, the ALFF of each voxel was further divided by the global mean of ALFF values for each subject within the default brain mask from the DPABI, with background and other non-brain tissue signals removed. This resulted in a standardized whole-brain ALFF map. For fALFF analyses, the sum of the amplitude values in the 0.01 to 0.08 Hz low-frequency power range was divided by the sum of the amplitudes over the entire detectable power spectrum in the range: 0.01–0.1 Hz. To calcuate ReHo, a KCC was assigned to a given voxel by calculating the KCC of times series of the voxel and the nearest 26 neighboring voxels (Zang et al., 2004). Higher ReHo values of a given voxel represent a higher degree of localized temporal synchronization within a neighboring cluster. Then, the voxel ReHo value was divided by the average ReHo value of the entire brain in each subject to guarantee the standardization. ReHo maps were eventually smoothed with a Gaussian kernel of 4-mm full width at half maximum.

5.2.5. Statistical analyses

Normality of cytokine levels was assessed with the Shapiro-Wilk test. Two-tailed t tests or Mann–Whitney U tests were used for continuous variables, and χ^2 tests for categorical variables. Statistical significance was set at $p < 0.05$. Paired-t tests were performed to test the differences between cytokines levels at baseline and follow-up. Between-group analyses of ALFF and fALFF values were

performed using voxel-based ANCOVA with sex and framewise displacement (FD) as covariates. Voxel-wise threshold was set at $p<0.001$ with FWE cluster-level correction $\alpha = 0.05$. Multiple regression analyses of PANSS scores (total and subscales) with ALFF and fALFF values and inflammatory markers as predictors were performed to test the relationship between peripheral inflammation, imaging measures and symptoms severity. Further exploratory analyses were conducted to test the correlation between imaging measures and cognitive scores. Statistical analyses were conducted using Jamovi (v 2.3.21.0) and SPSS (v 20.0.1.1).

5.3. Results

5.3.1. Demographic and clinical characteristics

In the full baseline sample (n = 207), neuroimaging data of 162 participants were available. At follow-up, data of 85 participants were available. A total of 22 and 11 subjects were excluded for excessive head motion from baseline and follow-up, respectively. In this sample, inflammatory markers were available for 132 participants at baseline and 63 at follow-up. In the baseline sample, the mean age was 26.9 ± 5.3 and there were more male participants (n = 95, 72%). At follow-up (12.2 ± 0.4 months), mean age was 27.6 ± 5.1 and there were 49 males and 14 females. BMI ranged from 16.3 to 60.2 at baseline, (n = 125, M = 28.1, *SD* = 7.2), and from 17.3 to 52.7 at follow-up (n = 60, M = 28.0, *SD* = 6.64). Participants were stratified according to their serum CRP levels into CRP < 3 mg/L (n = 85, CRP = 0.94 ± 0.76 mg/L) and CRP ≥ 3 mg/L (n = 47, CRP = 7.41 ± 4.87 mg/L). Age and BMI were significantly lower in participants with CRP < 3 mg/L compared to participants with CRP ≥ 3 mg/L. Characteristics of the samples are shown in the Appendix.

5.3.2. Inflammatory markers analysis

Inflammatory markers were available for 199 participants at baseline and 105 at follow-up. In the overall sample, IL-1 RA (t=-2.71, p=0.007) and IL-13 (t=-2.37, p=0.020) were significantly lower at follow-up compared to baseline. In the group randomized to minocycline, IL-6 levels (t=-2.32,

p=0.024) were lower at follow-up compared to baseline, while in the placebo group IL-1 RA levels (t=-1.96, p=0.054) at follow-up showed a reduction compared to baseline. No differences in CRP and cytokines levels at follow-up between FEP randomized to minocycline and placebo were observed (all p>0.05). Both at baseline and follow-up, CRP levels were positively correlated with IL-6 levels (rho=0.52, p<0.001 and rho=0.49, p<0.001, respectively) (Fig. 24). A positive correlation between CRP levels and IL-6 levels was observed both in the male group (rho=0.50, p<0.001) and in the female group (rho=0.56, p<0.001).

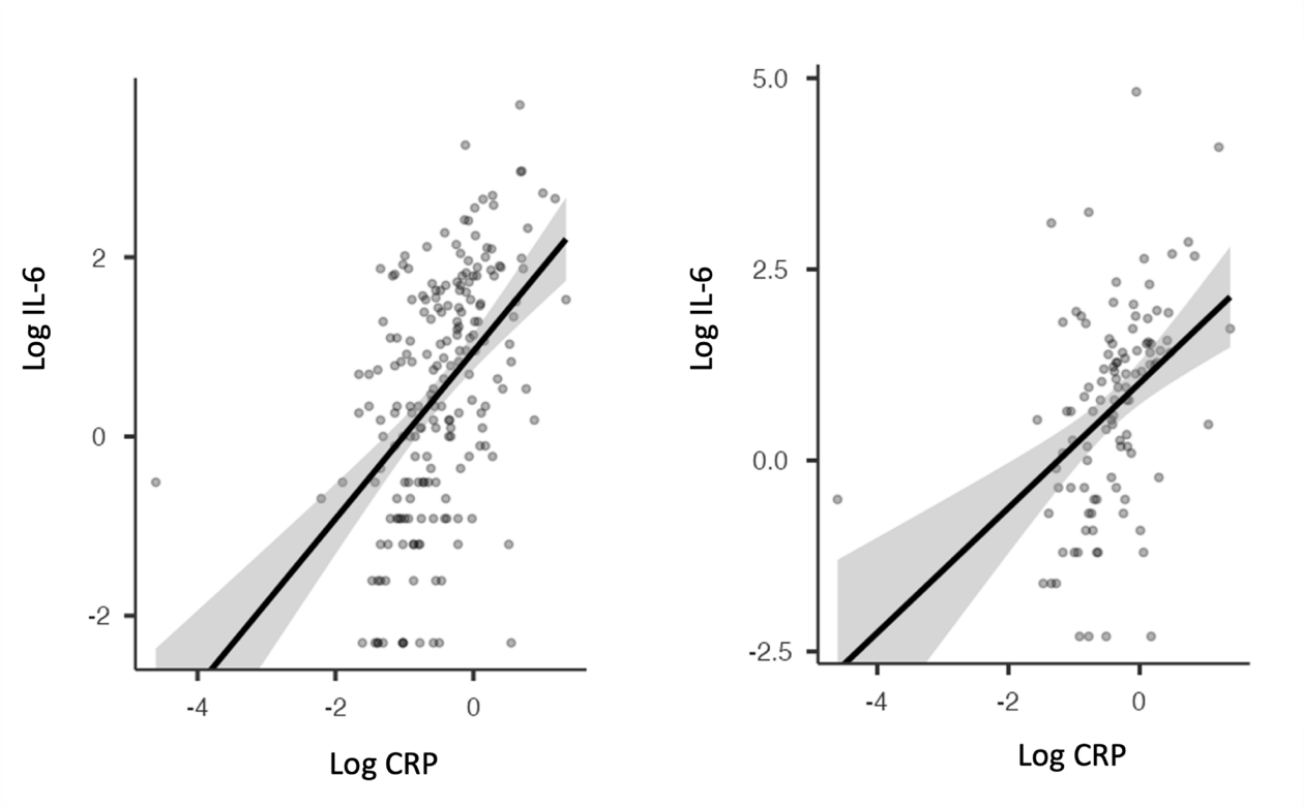

Figure 24: Scatter plots of CRP and IL-6 levels**.** Fig. a) Baseline correlations between CRP and IL-6 levels; Fig. b) Follow-up correlations between CRP and IL-6 levels.

5.3.3. Group differences in spontaneous brain activity at baseline

In the baseline sample, FEP with CRP ≥ 3 mg/L had higher ALFF in the right superior frontal gyrus (SFG) (x,y,z=21,63,12) and left cerebellum (x,y,z=-36,-42,-51) compared with FEP with CRP < 3 mg/L (Fig. 25a). In addition, FEP with CRP ≥ 3 mg/L presented lower fALFF values in two clusters of the right postcentral gyrus (x,y,z=69,-15,45; x,y,z=30,-27,75) and left precentral gyrus (x,y,z=-18,-24,78) compared to FEP with CRP < 3 mg/L (Fig. 25b).

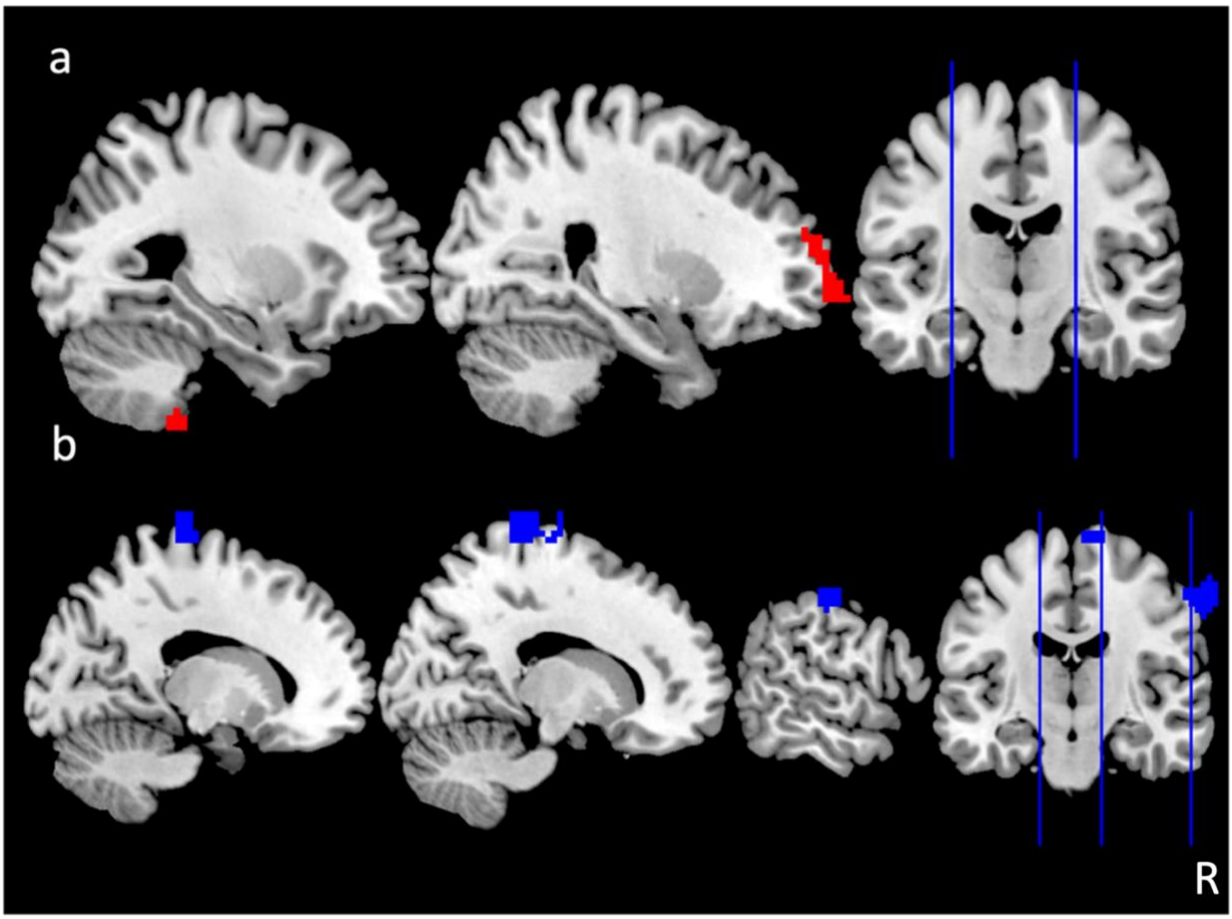

Figure 25. Group differences in spontaneous brain activity in individuals with FEP. Fig. a) Brain areas with higher ALFF in FEP with CRP ≥ 3 mg/L (low inflammation) compared to FEP with CRP < 3 mg/L (no inflammation); Fig. b) Brain areas with lower fALFF in FEP with CRP ≥ 3 mg/L (low inflammation) compared to FEP with CRP < 3 mg/L (no inflammation). Significance level was set at false discovery rate corrected $p < 0.05$. Blue and red denote increased and decreased ALFF and fALFF values in the FEP, respectively. All images are thresholded with $p<0.005$, and a spatial extent of 10 voxels. R = right.

5.3.4. Association between imaging measures and symptoms severity

At baseline, there was no relationship between measures of spontaneous brain activity in the clusters identified in our analysis and symptoms severity (PANSS total and subscales: all $p > 0.05$). However, exploratory analyses showed a negative correlation between ALFF values of the right SFG and AVLT scores (rho=-0.247, p=0.006) (Fig. 26).

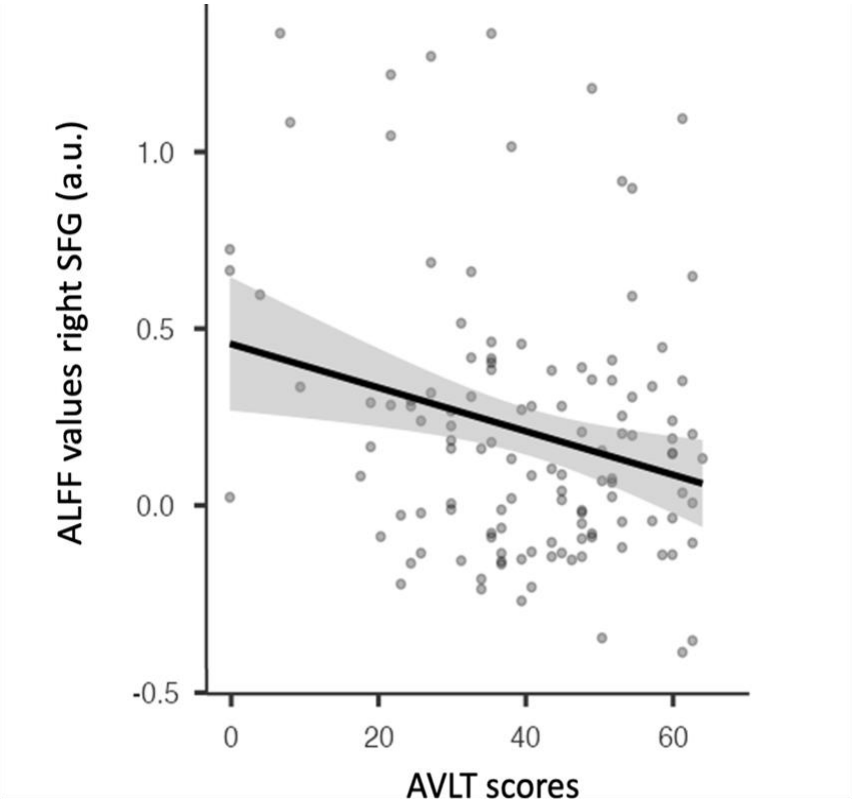

Figure 26. Scatter plots of ALFF values in the right SFG and and AVLT scores among among FEP. a.u. = arbitrary units.

5.3.5. Group differences in spontaneous brain activity at follow-up

The significant ALFF and fALFF differences between FEP with CRP < 3 mg/L and CRP ≥ 3 mg/L observed at baseline were not evident at follow-up, either in the minocycline or the placebo group. At an exploratory level, we explored group differences in spontaneous brain activity at the whole-brain level, but no significant results were observed. Furthermore, we tested ALFF and fALFF differences between FEP with CRP < 3 mg/L and CRP ≥ 3 mg/L in the minocycline and in the placebo group, but we found no statistically significant results.

5.4. Discussion

In this study we explored the association between peripheral inflammation and spontaneous brain activity in a sample of individuals with FEP. Three main results emerged: a) FEP with CRP ≥ 3 mg/L had higher ALFF in the left cerebellum and right SFG and lower fALFF in the right postcentral gyrus and left precentral gyrus compared to FEP with CRP < 3 mg/L; b) no relationships between peripheral

inflammation markers and measures of spontaneous brain activity and symptoms severity were observed, although at an exploratory level we found a negative correlation between right SFG ALFF values and AVLT scores; c) minocycline did not influence the association between peripheral inflammation and spontaneous brain activity.

5.4.1. Inflammation-related alterations in spontaneous brain activity

Consistently with our hypothesis, this study revealed an association between peripheral inflammation and spontaneous brain activity in the right SFG. Interestingly, our results align with previous literature on spontaneous brain activity changes associated with peripheral inflammatory status. In particular, a study conducted on patients with Crohn's disease reported significantly higher ALFF values in the left SFG in patients compared with controls, in addition to higher ALFF in the anterior cingulate cortex and supplementary motor area (Li et al., 2021). Also, patients with chronic rhinosinusitis, a multi-factorial disease influenced by chronic inflammation and aberrant immunity, presented significantly increased ALFF in the left SFG compared with HC. In this study, the severity of inflammation as well as anxiety and depression symptoms were positively correlated with ALFF values in the left SFG (Lin et al., 2023). Similar increases in ALFF in frontal areas have also been described in ulcerative colitis, where patients exhibited higher ALFF in the left middle frontal gyrus compared to controls (Fan et al., 2019). Differently, a trial that explored ALFF changes in 20 healthy subjects after either a Salmonella typhi vaccine or a placebo saline injection demonstrated that the vaccine was associated with lower ALFF in the right and left frontal pole, right superior, middle and inferior frontal gyrus and paracingulate gyrus (Stefanov et al., 2020). In addition, individuals with ankylosing spondylitis, a chronic inflammatory rheumatic disease, presented higher ALFF in the left cerebellum, left middle temporal gyrus, left superior occipital gyrus, left postcentral gyrus and the right precuneus and lower ALFF in the left medial frontal gyrus, the right precentral gyrus and the right posterior cingulate, (Li et al., 2017). Overall, this evidence indicates that an increase in peripheral inflammation might result in changes in prefrontal spontaneous activity, regardless of the

individual's underlying disorder. In FEP, we did not detect any association between psychopathology evaluated with the PANSS and inflammation-related abnormalities in the SFG, but we found a negative correlation between ALFF values of the right SFG and AVLT scores, indicating that prefrontal alterations might be implicated in cognitive deficits in FEP.

Furthermore, we observed an increase in ALFF in the left cerebellum in FEP individuals with higher levels of inflammation. In a recent study on task-based alterations in medication-free adolescents with psychiatric symptoms, CRP levels presented a positive correlation with cerebellar activation (Liu et al., 2020), which might indicate the cerebellum as a possible site of inflammation-related dysfunctions in FEP. However, only limited evidence on the effect of inflammation on cerebellar function is available, so future studies are warranted to elucidate this potential association.

Differently, lower fALFF values were observed in FEP with higher levels of inflammation in the precentral and postcentral gyrus, areas primarily implicated in the control of voluntary movements and in the identification of somatic sensations (Chen et al., 2008; Semmes and Chow, 1955). Previous research on rheumatic disorders reported altered cerebral blood flow in the precentral gyrus (Fang et al., 2022), suggesting that functional abnormalities at this level might be implicated in movement disorders. Interestingly, non-specific, subtle disturbances in motor and sensory performances, also referred to as neurological soft signs (NSS), have been commonly reported in FEP and SCZ (Bachmann and Schröder, 2018). In SCZ, NSS seem to be associated with changes in the cortical-subcortical-cerebellar circuit, including the SFG, precentral gyrus, postcentral gyrus and cerebellum (Kong et al., 2020; Zhao et al., 2014). Crucially, functional effects of peripheral inflammation on brain regions relevant to motor activity have been consistently revealed by fMRI in subjects administered inflammatory cytokines or inflammatory stimuli (Goldsmith et al., 2023). Although no direct observation of an association between NSS and inflammatory status has been reported so far, we might speculate that increased levels of peripheral inflammations in FEP might influence brain areas implicated in sensory and motor functions, and might ultimately lead to the development of NSS. Future research aimed at testing this hypothesis could clarify the association between

inflammation and sensory-motor function in psychosis and may help identifying new treatment targets.

5.4.2. Role of minocycline on spontaneous brain activity

Despite the promising results of early studies on minocycline in psychosis, the randomized, placebo-controlled multicentric BeneMin trial reported no evidence of an effect of minocycline treatment for up to 1 year on the progression or severity of negative symptoms within the first 5 years of the disorder (Deakin et al., 2018). A subsequent study by the same research group showed that minocycline did not affect any individual negative symptom or sub-domain in the full sample of FEP or in the immune active sub-group defined by CRP levels between 1 and 10 mg/l (Krynicki et al., 2021). Our negative results align with these findings and indicate that minocycline not only does not exert an effect on clinical symptoms, but also does not influence spontaneous brain activity, and this holds true also in the group with increased levels of peripheral inflammation. Crucially, we did not find any difference in CRP and cytokines levels between FEP randomized to minocycline and placebo, which indicates that the use of minocycline was not associated with a decrease of peripheral pro-inflammatory markers or an increase in anti-inflammatory markers.

5.4.3. Limitations

This study presents some limitations. First, we did not include a healthy control group, so we were not able to test the differences in inflammation-related spontaneous brain activity between patients and heathy individuals. Second, antipsychotic and antidepressant medications have not been included as a co-variate in the analysis, as this information was not available for all the subjects. However, the most commonly prescribed medication was olanzapine followed by risperidone, aripiprazole and amisulpride. Antidepressants were also prescribed in around 20% of patients. This raises another potential limitation, since antidepressants may impact peripheral cytokine levels. Third, the study had a high drop-out rate, although in line with longitudinal studies of psychosis, which resulted in a

considerable imbalance between the baseline and follow-up sample. Lastly, the mean CRP levels were generally low in the group as a whole compared with previous research.

5.5. Conclusions

In conclusion, we found that increased peripheral inflammation was associated to changes in prefrontal spontaneous activity in FEP, and these abnormalities correlated with worse verbal learning and memory performances. Also, inflammation was linked to altered intrinsic activity in the prefronto-precentral-postcentral-cerebellar circuit, which is implicated in sensory-motor functions. Although speculatively, we hypothesize that increased levels of peripheral inflammations in FEP could lead to the development of NSS. Future research aimed at testing this hypothesis might clarify the association between inflammation and sensory-motor function in individuals at different stages of the disorder and may help identifying new treatment targets. Lastly, we observed that minocycline did not influence spontaneous brain activity, not even in the group with increased levels of peripheral inflammation.

CHAPTER 4: SCHIZOPHRENIA AND BIPOLAR DISORDER

STUDY 5: DYNAMIC FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A SYSTEMATIC REVIEW OF THE EVIDENCE AND ASSOCIATIONS WITH PSYCHOPATHOLOGICAL FEATURES

6.1. Introduction

After a FEP, the psychotic disorder can transition to a chronic disorder, characterized by phases of relapse with remissions and, in certain cases, to a chronic treatment-resistant unremitting disorder (Prakash et al., 2021). Among all diagnosis in FEP, the diagnoses that are most stable across time are SCZ and BD (Salvatore et al., 2009). SCZ and BD are severe disorders with significant overlap in many features, including genetic susceptibility (S. H. Lee et al., 2013b; Smoller et al., 2013) and clinical manifestations (Bambole et al., 2013; Lee et al., 2015). Both disorders have been associated with neural changes, mainly involving the fronto-thalamo-striatal and limbic regions (Cattarinussi et al., 2022; C. H. Chen et al., 2011b; Leroy et al., 2020; Minzenberg et al., 2009; Wu and Jiang, 2020). Rs-fMRI studies have described altered functional connectivity at rest, suggesting the presence of alterations of brain intrinsic activity (M. H. Lee et al., 2013). During rest, several brain regions show synchronous low-frequency oscillations of the BOLD signal (Fransson, 2005), that suggest a high level of FC between them (Menon, 2011a; Raichle, 2011; Smith et al., 2009). Importantly, these functionally connected areas, referred to as resting-state networks, correspond with brain networks recruited during the performance of a task (Biswal et al., 1997).

FC alterations of resting-state networks, particularly the DMN, the SAL and the EXE have been reported in association with several clinical features in both SCZ and BD (Hare et al., 2019; Lee et al., 2018; Menon, 2019; Sambataro et al., 2021a; Whitfield-Gabrieli and Ford, 2012). According to

the triple network model first proposed by Menon (Menon, 2011), the interaction between these network supports cognition, affective functions and goal-directed behaviors. Specifically, the EXE is active during high-order cognitive functions, the DMN is temporally anti-correlated with the EXE and contributes to vigilance, rumination, self-processing and learning (Buckner et al., 2008), and the SAL mediates the switching between these two networks (Menon, 2011). Furthermore, the SM, VIS, AUD, language, emotional and basal ganglia networks have been consistently described at rest in healthy subjects and in individuals with neurological or psychiatric disorders (Jimenez et al., 2019a; O'Donoghue et al., 2017a).

Early rs-fMRI studies worked under the assumption that the FC had spatial and temporal stationarity, thus supporting the notion that the average FC was representative of the FC of the brain. However, brain activity changes dynamically depending on demands, e.g., sleep, sedation, task performance (Bharath et al., 2017; Harvey et al., 2011), and is also true at rest, when multiple mental activities can occur (Allen et al., 2014). Therefore, while studies operating under the assumption of stationarity have greatly helped to identify resting-state networks and to understand the FC metrics of the brain, they have not been able to capture the complex dynamic changes of brain activity (Hutchison et al., 2013). Therefore, it has been suggested that the study dFC describing the time-varying aspects of FC, may provide greater insight into the functioning of the brain (Allen et al., 2014; Hutchison et al., 2013).

Several measures can be used to describe the dFC properties, including functional connectivity strength (FCS), which is a measure of dynamic connectivity calculated as the time-varying sum of connections between a brain voxel and all other voxels and describes the magnitude of signal coupling between brain regions or networks over time in a specific state (Yu et al., 2013). In addition, measures of stability and predictability of dFC, such as variability, flexibility, entropy and global efficiency, are also commonly employed. In detail, the variability of a specific brain region reflects its dynamic changes over time within brain states and is generally estimated by the overall variance of the dFC between networks/regions (J. Zhang et al., 2016). Differently, flexibility refers to the dynamic

reconfiguration of functional connections between different brain areas that occurs over time and for different tasks (Garcia et al., 2018; Harlalka et al., 2019). Flexibility can be measured in the context of entropy, which is an index of complexity that characterizes nonlinear properties of resting-state signal (Sokunbi et al., 2011; Wang et al., 2014). Lastly, global efficiency measures the efficiency of information exchange over time in a temporal network (Dai et al., 2016).

Numerous studies exploring dFC have been conducted in recent years in SCZ and BD. However, current literature is affected by considerable heterogeneity, and the clinical utility of dFC has not been fully clarified. In this context, we decided to systematically summarize and analyze the available studies on dFC at rest in SCZ and BD to identify disease-associated changes. In addition, we wanted to shed a light on the association between dFC metrics and symptomatologic dimensions in SCZ and BD, with the final goal to clarify the role of dFC alterations in the development of psychopathology in the SCZ – BD spectrum.

6.2. Methods

6.2.1. Article selection and classification

In February 2022, we conducted a search on PubMed, Scopus, and Web of Science of the original papers published in peer-reviewed journals without any language restriction, following the MOOSE guidelines (Brooke et al., 2021). A combination of the following keywords was used: “dynamic functional connectivity” OR “dynamic functional network connectivity” OR dFC OR “dynamic network connectivity” OR “dynamic brain network” OR “dynamic brain functional network” OR “dynamic brain connectivity” AND schizophrenia OR bipolar disorder OR BD or psychosis. We also included relevant studies appearing in the reference lists of the selected articles.

Studies were included if they: 1) estimated dFC; 2) investigated individuals affected by BD or/and SCZ; 3) included a healthy control (HC) comparison group. The initial search resulted in 411 articles. The number of duplicates was 198 studies. After reviewing the abstracts of these articles, 123 studies

were selected for full-text reading and 43 studies were further excluded because they did not meet the inclusion criteria. Finally, a total of 77 studies were selected (see Fig. 27).

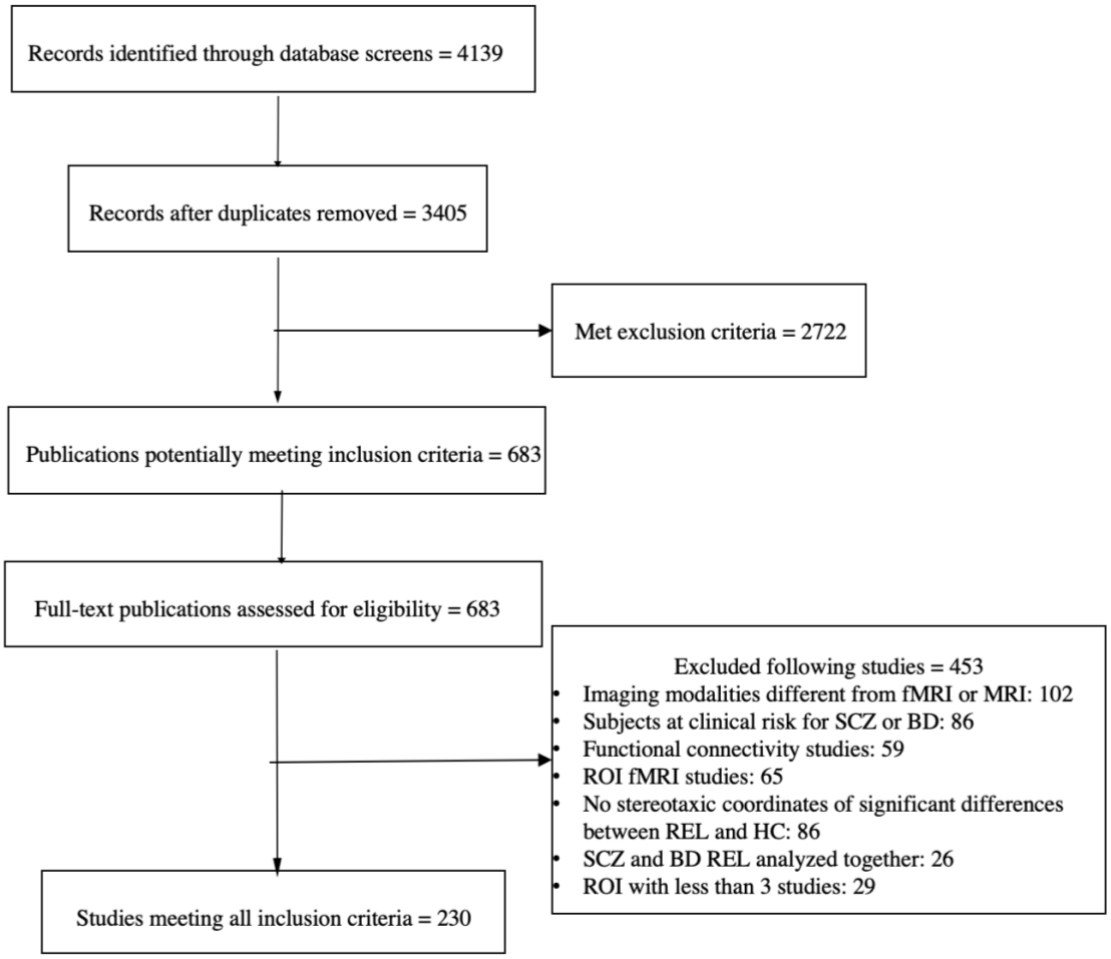

Figure 27. PRISMA flowchart for the review of imaging articles in SCZ and BD.

6.3. Results

6.3.1. Studies characteristics

Overall, 54 studies were conducted in SCZ, 16 in BD and seven in both. All but four studies (Duan et al., 2020; Lottman et al., 2017; Wang et al., 2021; Zhang et al., 2021) had a cross-sectional design. Within SCZ studies, a study was conducted in patients with FEP (Briend et al., 2020), while two investigations included early-stage SCZ with a duration of the illness of approximately two years (Du et al., 2018a; Mennigen et al., 2019). Three investigations explored alterations in dFC in SCZ and in

their unaffected relatives (Braun et al., 2016; Guo et al., 2018; Su et al., 2016) and two studies also included individuals at high clinical risk of psychosis (CHR) (Du et al., 2018a; Mennigen et al., 2019). Most studies were conducted at rest, and only in five studies dFC was calculated during the performance of a task (Braun et al., 2016; Gifford et al., 2020; Li et al., 2020; Sakoğlu et al, 2010; Yue et al., 2018). Eleven studies were carried out on the same sample (Damaraju et al., 2014; Faghiri et al., 2021, 2020; Fu et al., 2021, 2018; Miller et al., 2016a, 2016b; Rahaman et al., 2021; Salman et al., 2019; Sendi et al., 2021a, 2021b).

Psychopathological evaluations were carried out using the following scales: the Brief Psychiatric Symptom Scale (BPRS) (Overall and Gorham, 1962), the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959), the Hamilton Depression Scale (HAM-D) (Hamilton, 1960), the Positive and Negative Affect Scale (PANAS-N) (Watson et al., 1988), the PANSS (Kay et al., 1987), the Scale for the Assessment of Negative Symptoms (SANS) (Andersen, 1989), the Scale for the Assessment of Positive Symptoms (SAPS) (Andersen, 1984), the Sign and Symptoms of Psychiatry illness (SSPI) (Liddle et al., 2002), the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Some studies also included functioning and cognitive assessments.

Image acquisition protocols, analytic methods and clinical assessment tools of the studies are summarized in the Tab. 1, 2 and 3 of the Appendix.

6.3.2. dFC techniques

First, fMRI time series were preprocessed, and then dFC analysis was performed with the following steps: 1) signal extraction to obtain meaningful metrics in terms of raw time series, low-frequency oscillations, regional connectivity, etc; 2) dFC calculation, where several time-dependent connectivity matrices are obtained across the whole time-series; and 3) the estimation of recurring and stable patterns of dFC states at the individual and group level (see Tab. 4 in the Appendix).

Signal extraction. The spatial group ICA was the most widely used technique to obtain time series (Calhoun et al., 2001). Furthermore, 19 studies explored FC with a seed-based approach (Wu et al., 2018). One study investigated the dynamics of ReHo (Dong et al., 2019), which studies the similarity of the time series of a particular voxel with the time series of neighboring voxels, providing a measure of localized FC (Zang et al., 2004). Spontaneous brain activity at rest can be measured with ALFF and fALFF (Turner et al., 2013). Here, we included studies that explored the dynamics of ALFF (dALFF) and dynamic fALFF (dfALFF), defined as recurring patterns of ALFF and fALFF variability over time calculated with the sliding window approach and clustered in states (Chen et al., 2022; Fu et al., 2018; He et al., 2021; Liang et al., 2020; Luo et al., 2021; Nyatega et al., 2021). Moreover, Yang et al. (2020) used voxel mirrored homotopic connectivity analysis to investigate the temporal variability of interhemispheric functional connectivity between homotopic areas (Yang et al., 2020).

dFC calculation. One of the most widely used technique to study time-varying changes in FC was the sliding window (SW) approach, which partitions the time course of the fMRI signal into several fixed temporal windows (that may partially overlap), where pairwise correlations between regions/networks are computed until reaching the end of the time courses itself (Hutchison RM et al., 2013; Rashid et al., 2014). Then, to assess the frequency and structure of reoccurring FC patterns, commonly a clustering algorithm for windowed covariance matrices is used (Lloyd, 1982) (Fig. 28).

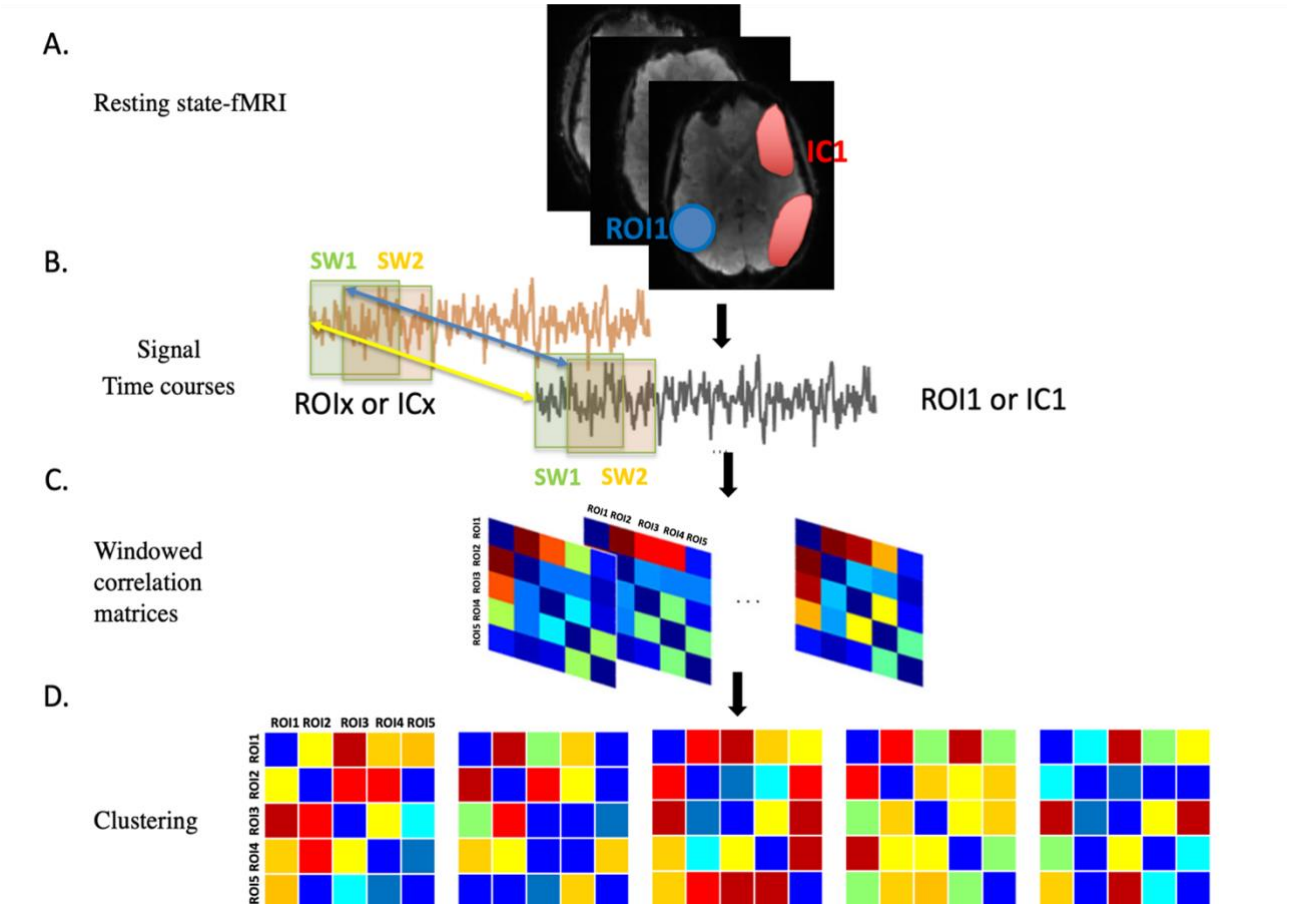

Figure 28. Estimation of functional network connectivity starts from A) the time series of regions of interest or independent component analysis or other measures from resting state fMRI data; B) the signal is then analyzed across several sliding windows to calculate the correlation between signals that is C) entered in correlation matrices; D) these matrices are clustered in connectivity states.

In addition, the following methods have been used: 1) network flexibility, which is a measure of how often a brain area changes its allegiance to a community of nodes over time (Braun et al., 2016); 2) quasi-periodic patterns (QPP), which reflect the spatio-temporal patterns of signal oscillations in the infra-low frequency range and are supposed to underlie functional connectivity (Briend et al., 2020); 3) filter-banked connectivity, an approach that does not make a priori assumptions about connectivity frequency and performs frequency tiling in the connectivity domain (Faghiri et al., 2021); 4) dynamic directional functional domain connectivity, a method that operates at a dimensional scale sufficient to capture multiplexed dynamical relationships within and between functional domains (Miller et al., 2016a).

Estimation of connectivity states. k-means clustering was one of the most widely used methods to modularize windowed connectivity patterns. Briefly, k-means clustering automatically partitions a data set into a predefined number (k) of clusters, typically spanning from 2 to 20 (Shakil et al., 2014; Supekar et al., 2019). Each state is mutually exclusive, and the time spent in a specific connectivity state is defined as dwell time. Also, the dFC was measured using spatio-temporal meta-state analysis. Recently, cross-domain mutual information (CDMI) that uses mutual information (i.e., mutual dependence between pairs of variables adopted from a measure from information theory) within the brain networks belonging to the same functional domain has been used to estimate dFC thus including linear and nonlinear relationships (Salman et al., 2017).

In the following paragraphs, we will report dFC changes in SCZ relative to HC, in BD relative to HC and then studies directly comparing dFC in SCZ and BD. For each network (DMN, EXE, SAL, SM, VIS, emotive, SC and other networks) we will first describe the magnitude of the dFC (FCS), then its variability and lastly its interaction with other networks.

A summary of changes in dFC in SCZ and BD in terms of FCS and variability is illustrated in Fig. 29.

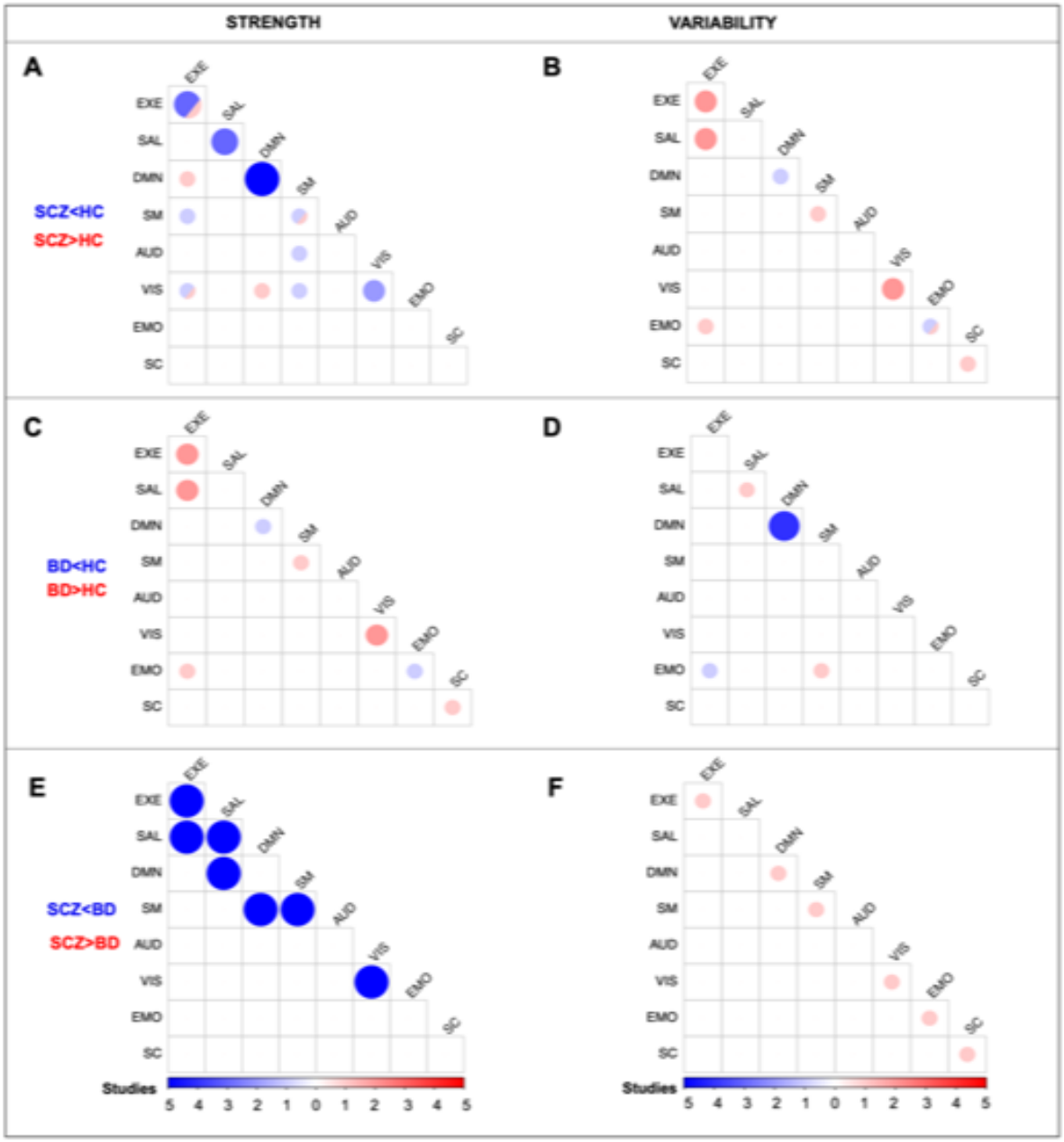

Figure 29. Dynamic Functional connectivity changes in SCZ and BD. Correlograms display differences in functional connectivity strength in SCZ (a), in BD c) relative to HC and between diagnosis (e) and in the dFC variability for SCZ (b), BD d) relative to HC and between diagnosis (f) for each cross-correlation in a lower triangular matrix. The color intensity and circle size reflect the number of studies reporting a difference, with red and blue color indicating greater and reduced dFC in the diagnostic groups relative to HC in the first two rows and in SCZ relative to BD in the last row, respectively. The color bar indicates the number of studies reporting a difference. In a circle, a sector with different color indicates contrasting results and each color reflects the number of studies supporting each direction. EXE, executive; SAL, salience; DMN, default mode network; SM, sensorymotor; AUD, auditory; VIS, visual; EMO, emotional; SC, subcortical.

6.3.3. dFC alterations in SCZ vs. healthy subjects

Global Connectivity. A general pattern of dynamic dysconnectivity between brain networks was reported in SCZ (Long et al., 2021). Consistent with this, mixed increases and decreases in dFC were described mainly in the triple network, cerebellum, VIS, SM and the subcortical network (Luo et al.,

2020). Importantly, several studies showed that SCZ spent less time in globally coherent and subcortical-centered states (Damaraju et al., 2014; Espinoza et al., 2019; Sanfratello et al., 2019; Zarghami et al., 2020) and in states with high within- and between-FC of sensory networks (Weber et al., 2020), while they dwelled longer in states characterized by strong FC within networks (in particular, the DMN and the language network) (Weber et al., 2020). Differently, Plis et al. (2018) showed that SCZ made significantly more transitions to states characterized by weaker connectivity within most brain networks (subcortical, AUD, VIS, SM, EXE, DMN and cerebellum) (Plis et al., 2018). A reduction in time-varying connectivity patterns in whole-brain networks was seen (Miller et al., 2016b; Rabany et al., 2019), particularly in patients with more severe hallucinations (Miller et al., 2016a). Moreover, SCZ presented increased entropy and CDMI, which is a measure of dependence across sets of related brain areas grouped for anatomical and functional associations, indicating reduced dynamic changes in brain FC (Mustafa S. Salman et al., 2019; Salman et al., 2017). Stepwise functional network reconfiguration (sFNR), a measure reflecting the global ability to rewire brain networks, was increased in large-scale brain networks, including SM, VIS, EXE and DMN, thus indicating a higher temporal variability of the networks and, therefore, their instability (Fu et al., 2021). Finally, when selectively investigating the low-frequency bands, SCZ had more occurrences of states characterized by weaker widespread dALFF patterns and fewer occurrences of strong dALFF states in most brain networks, particularly the AUD, SM, VIS, and subcortical networks (Fu et al., 2018).

Default mode network. Within-DMN dFC was reduced (Du et al., 2016; Luo et al., 2020; Salman et al., 2019; Sendi et al., 2021a), although posterior DMN (i.e., right medial parietal cortex) showed increased temporal global efficiency (Sun et al., 2019). The variability of DMN was reduced (Dong et al., 2019). Furthermore, synchronizability, modularity, recurrence, and consistency of the statelets in the DMN were decreased, suggesting that SCZ exhibit more erratic and less efficient communication between the DMN and other brain networks (Rahaman et al., 2021). Between-

network dFC revealed that SCZ dwelled in or switch to a state with high positive connectivity between DMN and EXE (Bhinge et al., 2019).

Executive and attention network. SCZ presented either a general reduction (Long et al., 2021) or an increase (Luo et al., 2020) in within-EXE functional FCS, and spent more time in states with weaker FCS in this network (Zarghami et al., 2020). The contribution of QPP to FCS was greater in EXE in FEP (Briend et al., 2020), suggesting a greater impact of QPP on intrinsic brain activity in these subjects. In contrast, the frontal cortex had a lower state-specific FCS in all the states (Sun et al., 2021) and higher temporal nodal efficiency, which assesses the efficiency of information transfer between nodes in a temporal network (Sun et al., 2019). Additionally, patients with SCZ demonstrated a decrease in state-specific FCS between EXE and the cerebellar motor cluster (He et al., 2019) and between EXE and VIS (Yang et al., 2022) Regarding variability measures, higher flexibility scores were reported in SCZ in the EXE (Gifford et al., 2020), along with increased voxel-wise, region-wise, and network-wise FC variability in the attention network (Dong et al., 2019).

Salience network. SAL FCS and within-network FC were reduced in different frequency bands (Luo et al., 2020). Between-network dynamic interactions of SAL-centered cross-networks within the "triple-network" model were significantly reduced, less persistent, and more variable in patients (Supekar et al., 2019, Wang et al., 2016).

Sensory-motor network. FCS was increased in the motor network (Y. Du et al., 2021), but showed high variability and reduced interaction with other networks. In particular, flexibility and variability were higher in the cerebellar, subcortical, and thalamic areas in SCZ (Gifford et al., 2020). Conversely, FCS between the motor and the EXE, DMN and SM (H. He et al., 2019), as well as between the SM and the VIS and AUD (Faghiri et al., 2021) was reduced. Additionally, SCZ dwelled less in states with the predominance of sensory and motor networks (Faghiri et al., 2020; Sendi et al., 2021a). Lastly, the synchronizability, modularity, recurrence, and consistency of the statelets were reduced (Rahaman et al., 2021).

Visual network. FCS was reduced in VIS (Sheng et al., 2021) and also between VIS and the EXE (Yang et al., 2022), AUD and SM networks (Salman et al., 2017), and the mirror system network (Sun et al., 2021). A higher sample entropy was observed in the right middle occipital gyrus (Jia and Gu, 2019), while the lateral occipital cortex showed an increased interaction with EXE and the thalamus at rest, and with DMN during task switching (Li et al., 2020). Synchronizability, modularity, recurrence, and consistency in VIS networks were reduced (Rahaman et al., 2021) and FC variability was increased in dorsal VIS (Deng et al., 2019).

Emotional network. The variability of FC variability was reduced within the emotional network (Deng et al., 2021), and increased between the amygdala-prefrontal network (Yue et al., 2018).

Subcortical and other networks. Higher flexibility scores (Gifford et al., 2020) and temporal global efficiency (Sun et al., 2019) were reported in subcortical areas. Decreased FCS was described reported between the olfactory cortex and the hippocampus, and this may be part of altered sensory integration patterns in this disorder (Y. Du et al., 2021).

6.3.4. dFC alterations in BD vs. healthy subjects

Global Connectivity. A heterogeneous picture of alterations in global dFC was observed in BD. The FCS between the right anterior insula and the right middle occipital gyrus and the left inferior parietal lobule was increased (Pang et al., 2018). Furthermore, in patients with BD in the depressive phase, the dynamic interhemispheric FC - the dFC between a given voxel and the corresponding homologous voxel in the contralateral hemisphere - was reduced in the superior parietal lobule, the angular gyrus, the precuneus, and increased in the cerebellum, orbitofrontal cortex, postcentral gyrus, superior temporal gyrus and supplementary motor area. Notably, increased dynamic interhemispheric FC in the postcentral gyrus was associated with more depressive episodes (Yang et al., 2020). When affective status was considered, depressed BD switched more between states and dwelled more in a state characterized by a negative correlation between the SAL, cerebellum, and the subcortical network and the SM, AUD and VIS, and less in a state characterized by negative correlations between

the DMN and other functional networks (Wang et al., 2020). Compared to MDD, unmedicated patients with BD-II showed greater variability in dFC between the dorsal striatal putamen and sensory-motor regions (i.e., left supramarginal area) and the ventral rostral putamen and the parietal cortex (i.e., right inferior parietal lobule), similarly to MDD, and between the dorsocaudal putamen and the motor regions (i.e., precentral gyrus) compared to MDD and HC (Chen et al., 2022). Lastly, a study conducted on euthymic BD reported an increased number of transitions between a high-level cognitive state and a low-level sensory state in BD (M. Du et al., 2021).

Default mode network. BD was associated with decreased network switching rate in the DMN (Han et al., 2020). In particular, reduced dFC was present in posterior DMN in depressed patients with BD (Luo et al., 2021), and specifically BD-I (Liang et al., 2020). Also, FCS between DMN (middle temporal gyrus and the postcentral gyrus) and SM (superior temporal gyrus) was reduced during depression relative to euthymia in BD (Liu et al., 2021). In BD-I, the FCS between the two hubs of the DMN (medial prefrontal cortex and posterior cingulate cortex) was less variable over time, indicating greater rigidity and this was associated with reduced cognitive performance (Nguyen et al., 2017a).

Executive network. dFC in the frontal-striatal-thalamic circuit was increased in euthymic BD (Liu et al., 2021) and in depressed BD relative to HC (Tang et al., 2022) and MDD and HC (Pang et al., 2020).

Salience network. Euthymic BD showed increased dFC variability of the right anterior insula. Notably, BD shared a reduced variability between the right ventral anterior insula and the ventrolateral prefrontal cortex with MDD and had the greatest variability of the dFC of the right dorsal anterior insula with temporo-occipital regions compared to MDD and HC (Pang et al., 2018).

Sensory-motor network. A state-dependent increase of FCS between SM and DMN, which was greater in depressed BD relative to euthymic BD relative to euthymic BD and HC, was reported by one study (Liu et al., 2021a).

Emotional network. Depressed BD presented changes in between-network FCS of the limbic system and precisely increased amygdala-cerebellar and decreased amygdala-postcentral gyrus dFC, respectively (Fateh et al., 2020). In addition, depressed BD had reduced dynamic regional phase synchrony, a measure of instantaneous coherence, in fronto-striato-limbic areas (Tang et al., 2022).

6.3.5. dFC differences between SCZ and BD

Studies comparing SCZ and BD indicated greater dysconnectivity in SCZ relative to BD, with a pattern of decreased within-network dFC in VIS, SM, SAL and EXE, and increased dFC between the VIS and the EXE, SAL and limbic networks, and decreased dFC between the SAL and EXE, DMN and SM, and EXE and DMN (Li et al., 2021). SCZ had more widespread dFC changes relative to BD, involving increased FC variability in the SM, VIS, attention, limbic and subcortical areas at the regional and network levels, as well as decreased regional FC variabilities in the DMN (Long et al., 2020). In line with this, a similar altered dFC pattern was reported in DMN, VIS, SM, and EXE in SCZ and BD, with a greater magnitude of changes in SCZ relative to HC (Rashid et al., 2014a). Increased parieto-parietal inter-hemispheric network dFC was greater in both SCZ and BD in the right hemisphere, and in BD only in the left hemisphere, respectively, compared to HC (Das et al., 2020). Furthermore, an increase in functional stability in VIS was reported in BD relative to SCZ, indicating a higher concordance of dynamic FC over time in these patients (Zhu et al., 2020). Within the SCZ – BD spectrum, a reduced dFC fronto-parieto-cerebellar circuit with increased dFC in corticothalamic networks was observed, and the magnitude of this dysconnectivity increased from HC to BD, schizoaffective disorder (SAD) and SCZ. SCZ, BD and SAD shared a decrease in FCS between the thalamus and cerebellum and an increase in FCS between the postcentral gyrus and the thalamus (Du et al., 2017). A follow-up study showed that BD and SCZ had similar dFC changes between VIS (i.e., cuneus) and the insula, the putamen and the supramarginal gyrus (Du et al., 2020b).

6.3.6. Brain-behavior correlations

PANSS positive. In SCZ, the PANSS positive score was associated with the variability of dFC and cross-domain mutual information (Dong et al., 2019; Salman et al., 2019) and sample entropy (Jia and Gu, 2019) of the VIS, in addition to dynamic time-varying measures of SAL (He et al., 2021; Supekar et al., 2019). Furthermore, a correlation was observed between PANSS positive scores and FCS of the left thalamus (Luo et al., 2020) and temporal regional efficiency in the left inferior orbitofrontal gyrus (Sun et al., 2019). In BD, SAD and SCZ, hypoconnectivity between postcentral and frontal gyri was negatively correlated with PANSS positive scores (Du et al., 2017).

PANSS negative. In SCZ, the PANSS negative scores were correlated with the variability of dFC and temporal regional efficiency (Deng et al., 2019; Sun et al., 2019), and the entropy (Jia and Gu, 2019) of VIS and abnormal FC variability (Dong et al., 2019). Additionally, an association was also observed between PANSS negative and FCS in the right insula and the left orbital inferior frontal gyrus (Luo et al., 2020) and the left cerebellum crus 1 (Wang et al., 2019). Moreover, negative symptom severity was associated with the probability of transition from a state with predominant anterior-to-posterior DMN (lower precuneus/posterior cingulate cortex and higher anterior cingulate cortex) FC relative to a state with reverse pattern (higher precuneus/posterior cingulate cortex and lower anterior cingulate cortex) (Sendi et al., 2021). Dwelling longer in a state characterized by sparse and weak connectivity predicted PANSS negative scores, with reduced DMN and VIS dFC predicting greater attention domain impairment (Yang et al., 2022). In a study conducted in adolescent-onset SCZ, reduced dFC between the left middle temporal gyrus and the left extrastriate visual area predicted increased emotional withdrawal evaluated with item 2 of PANSS negative (Sun et al., 2021). Lastly, hypoconnectivities linking postcentral and frontal gyri were negatively correlated with the PANSS negative scores in BD, SAD and SCZ (Du et al., 2017).

PANSS general. Scores of general psychopathology were correlated with dynamic measures of the nodes of the VIS (Jia and Gu, 2019) VIS, SM and thalamus (Dong et al., 2019), left inferior orbitofrontal gyrus (Sun et al., 2019), right supramarginal gyrus (Wang et al., 2019), right amygdala

and left inferior parietal gyrus (Jia et al., 2017). PANSS total. The FCS of the cortico-thalamic circuits (Luo et al., 2020), temporal (Sun et al., 2019) and striato-parietal networks (Wang et al., 2019), reduced dALFF of the SAL-EXE connection (He et al., 2021) and increased variability of dFC of the frontal-amygdala connection (Yue et al., 2018) were associated with a higher PANSS total score, thus supporting the dysconnectivity hypothesis of SCZ (Yue et al., 2018). Additionally, the overall symptom severity was associated with the greater probability of transitioning from a state with predominant anterior-to-posterior DMN FC relative to a state with reverse pattern (Sendi et al., 2021b). The FC variability of VIS (Deng et al., 2019) and VIS, SM, and thalamus (Dong et al., 2019) was associated with a higher PANSS total score.

The correlations between PANSS scores and dFC measures are summarized in Tab. 5 of the Appendix.

Other symptoms scales. In SCZ, trait hallucination proneness over 1 year showed a significant association with dwell times in a state characterized by strong positive FC within the DMN and negative FC between the DMN and the insula (Weber et al., 2020), while hallucination severity measured with BPRS was positively correlated with the temporal instability of lateral occipital cortex connectivity (Li et al., 2020). Additionally, illness duration was associated with the entropy of the VIS (Jia and Gu, 2019), cortico-limbic networks (Jia et al., 2017). In depressed BD, depression severity (HAMD score) was positively correlated with the dFC between the right anterior insula and inferior parietal lobule (Pang et al., 2018) and with dwelling in a state with decreased FC between DMN, SAL, and EXE (Wang et al., 2019). Moreover, in depressed BD, the abnormal dynamic FCS in the frontal–striatum–thalamic circuit predicted anhedonia measured with the Snaith-Hamilton Pleasure Scale (Pang et al., 2020). Disorganization evaluated with the SSPI was associated with dFC in the SCZ, but not in BD (Das et al., 2020). The correlations between clinical scales and dFC measures are summarized in Tab. 5 of the Appendix.

Cognitive performances. Four studies explored the relationship between dFC measures and cognitive performance in SCZ and BD (Tab. 6 of the Appendix). In SCZ, dwell time in a state with positive FC

within the middle temporal gyrus and between the middle temporal gyrus with other regions predicted visual learning memory (Sendi et al., 2021). The variability of FC in cortico-limbic circuits was associated with poorer performance on the digit symbol coding task (Yue et al., 2018), while the temporal instability of LOC connectivity predicted higher switching costs during task performance in SCZ (Li et al., 2020). In BD, reduced connectivity variability within the DMN was associated with slower processing speed and impaired set-shifting (Nguyen et al., 2017a).

6.4. Discussion

This systematic review aimed at summarizing all available evidence on resting-state dFC alterations in the SCZ - BD spectrum and their association with psychiatric symptoms and behavior. We highlighted a global alteration of dFC in SCZ, while a more heterogeneous picture was found in BD. However, in both disorders, dysfunction of the triple network emerged. A direct comparison between SCZ and BD confirmed a predominant pattern of dysconnectivity in the triple network in SCZ. in Almost all the studies on SCZ showed an association between dFC metrics and psychopathological measures, in particular positive and negative symptoms.

6.4.1. Schizophrenia

Overall, the findings of our review show a consistent pattern of dFC alterations in SCZ compared to HC, involving abnormal FCS and an increased dwell time and transitions to states characterized by weaker connectivity within and between all major resting-state networks.

The dysconnectivity theory, postulated to explain the core psychopathological characteristics of SCZ, was first described in the 1990s. According to this theory, abnormal functional integration between anatomically distinct brain regions is at the core of SCZ symptomatology (Friston and Frith, 1995; Stephan et al., 2009). Importantly, SCZ is characterized by both global dysconnectivity and alterations at the topographic level in lower-order sensory and higher-order cognitive regions that may underlie sensory and cognitive symptoms (Yang et al., 2014; Zhang and Northoff, 2022).

Accordingly, dFC alterations in the triple network have been suggested to play a prominent role in the pathogenesis of SCZ (Dong et al., 2018; Menon, 2011). Interestingly, structural and functional alterations in SAL have been commonly associated with impaired attribution of salience to stimuli, which, in turn, is associated with delusions and hallucinations in SCZ (Palaniyappan et al., 2011). Furthermore, altered FC between SAL, EXE and DMN has been associated with positive and negative symptoms (Hare et al., 2019; Manoliu et al., 2014). In our review, alterations in dFC involving areas of the triple network appeared to be associated with psychotic symptoms in SCZ (Dong et al., 2019; He et al., 2021; Luo et al., 2020; Salman et al., 2017; Sun et al., 2019). Among these, Supekar et al. (2019) showed a positive association between the lack of dynamic engagement of the SAL with the EXE and DMN and disorganized thought (Supekar et al., 2019). Overall, our results suggest that patients with SCZ present a reduction in dFC metrics in the triple network, which may underlie psychotic symptoms for altered salience attribution, negative symptoms for altered DMN persistence, and cognition for impairment of EXE FC. In addition, abnormalities in dFC were reported in sensorimotor circuits, particularly in the VIS (Deng et al., 2019), AUD (Geng et al., 2020) and SM (Sambataro et al., 2021b), suggesting that altered FC metrics in these areas could be associated with deficits in the processing of external stimuli, which may lead to psychotic symptoms (Kubera et al., 2019; Thoma et al., 2016). In particular, abnormalities in the VIS and AUD pathways have been commonly reported in SCZ (Harvey et al., 2011; Kaufmann et al., 2015), and appear to be associated with hallucinations and negative symptoms (Orliac et al., 2017).

Interestingly, several studies have shown a relationship between changes in SM network dynamics and psychopathological measures, such as PANSS total (Deng et al., 2019; Dong et al., 2019), general (Dong et al., 2019; Jia and Gu, 2019) and negative scores (Deng et al., 2019; Jia and Gu, 2019; Wang et al., 2019). Furthermore, changes in dFC in sensory networks showed a correlation with positive symptoms evaluated with PANSS (Dong et al., 2019; Jia and Gu, 2019; Salman et al., 2017; Sun et al., 2019), as well as with hallucination severity measured with BPRS (Li et al., 2020). These results align with the spatiotemporal model of psychopathology proposed by Northoff and Duncan,

according to which temporal and spatial changes in spontaneous brain activity alter cognitive and affective processing in SCZ (Northoff, 2015; Northoff and Duncan, 2016). In particular, abnormalities in the SM and the sensory networks dFC could be associated with altered perceptions of spatial relationships with respect to the body and the environment in patients with SCZ, which might lead to delusions and hallucinations. Furthermore, as previously demonstrated in depression (Northoff, 2016), affective and cognitive symptoms such as anhedonia could be the phenotypic manifestation of spatiotemporal disturbances of the activity of the resting state that in SCZ appear to be prevalent in the VIS network, frontal areas, insula, and cerebellum.

6.4.2. Bipolar disorder

A more heterogeneous picture arose from studies conducted in patients with BD. The dFC abnormalities involved a wide range of cortical and subcortical areas, including frontal areas, limbic lobe, basal ganglia and thalamus, along with large brain networks, such as DMN, EXE, SAL and SM. Our results are in line with static rs-fMRI investigations that showed that BD was characterized by hypo and hyperconnectivity within the DMN, affective, EXE, ventral attention, sensorimotor and thalamic networks (Gong et al., 2021). In particular, in BD we found that the anterior insula, which is a key node of the SAL, had greater FC to the inferior parietal cortex, a node of the EXE, and reduced FC to the right ventrolateral FPC, which is another important region of this network for the control of cognition and impulsivity. Additionally, the DMN showed reduced integrity and modulation both in terms of lower network switching and reduced connectivity between its subnetworks, reduced dALFF, and altered interplay with anticorrelated networks, including EXE and SM. Abnormal thalamocortical connectivity may be a part of EXE dysfunction and may contribute to emotional dysregulation (Ramsay, 2019), which is a prominent feature of this disorder (Miola et al., 2022). Altered connectivity of the SAL can result in impaired cognition-emotion interaction and therefore contribute to the well-known mood and cognition impairments reported in BD (Ellard et al.,

2019). Furthermore, altered amygdala connectivity has been extensively studied in BD for its role in emotional processing and for its widespread interaction with brain networks (Rey et al., 2021a). Abnormal FC of the amygdala may contribute to the pathogenesis of emotional and behavioral symptoms that are present in BD (Luo et al., 2018) by: 1) increased FC with the cerebellum, which has been implicated not only in sensorimotor function but also in emotion and motivational processing and in several psychiatric disorders (Phillips et al., 2015), 2) reduced FC with the somatosensory cortex that could be responsible for the interaction between emotion and motor control and its subjective experience (Toschi et al., 2017). Remarkably, these functional coupling changes were also present in studies focused only on BD-I, which is more closely related to SCZ, suggesting partial shared pathophysiological mechanisms for these disorders (Trevisan et al., 2022). These heterogeneous results could be explained by the manifold clinical characteristics of patients with BD, both in terms of mood state (i.e., depression, euthymia, mania), presence/absence of psychotic symptoms and duration of the disease. Interestingly, half of the studies that explored the correlations between dFC metrics and psychopathology observed an association with depressive symptoms evaluated with HAMD (Pang et al., 2018; J. Wang et al., 2019) and the severity of anhedonia (Pang et al., 2020), while the others did not.

6.4.3. Disorder-specific changes

Investigations comparing dFC in SCZ and BD showed that these disorders present commonalities in the dFC alterations, albeit these are more pronounced in SCZ compared to BD. Notably, studies exploring the association between psychopathology and dFC in BD and SCZ showed that dynamic FC parameters in SCZ were correlated with the disorganization evaluated with the SSPI scale in the SCZ group, while no correlations were observed in the BD group (Das et al., 2020). Interestingly, a correlation was observed between PANSS scores and dFC in BD, SAD and SCZ (Du et al., 2017a). dFC metrics were also correlated with cognitive performance in SCZ and BD, suggesting that brain dynamics could be involved not only in the development of psychopathology but also in cognition.

6.4.4. Altered connectivity and signaling pathophysiological models

Dopamine has been associated with the dynamics of brain networks for its role in stabilizing cortical responses through the modulation of cortical pyramidal neurons and GABA-inhibitory interneurons. (Sambataro et al., 2009) Furthermore, this neurotransmitter can modulate the frequency of membrane oscillations and result in increased synchronization within large-scale networks (Seamans and Yang, 2004). Increased presynaptic dopamine signaling has been implicated in SCZ, in the so-called "dopamine hypothesis" and similarly, albeit of a small magnitude, increased D2/D3 availability and striatal dopamine amino transporter levels have been reported in BD (Ashok et al., 2017). Furthermore, glutamate signaling (particularly N-methyl-d-aspartate, NMDA) has also been implicated in modulating brain dynamics. Braun et al. (2016) showed in HC that during working memory processing dextromethorphan, an NMDA-receptor antagonist can increase network flexibility, a measure of the ability to reconfigure a node within a network that suggests temporal disorganization of the community structure of the brain. Similar hyperflexibility was also found in SCZ (Braun et al., 2016). In particular, altered glutamatergic signaling with hypoactivity of the NMDA system in excitatory pyramidal cortical cells and in fast-spiking GABA inhibitory interneurons can affect the synchrony of brain oscillations and their discharge, ultimately translating into reduced stability of brain networks (Uhlhaas and Singer, 2010) and can result in positive, negative and cognitive symptoms of SCZ (Merritt et al., 2013). Converging evidence from preclinical and clinical studies suggests an increased activity of NMDA in BD, with mood stabilizers modulating this glutamatergic signaling (Konstantinos N. Fountoulakis, 2012). Pharmacological studies with NMDA antagonists, including ketamine and memantine, have shown some efficacy in BD depression (Delfino et al., 2020). Furthermore, antipsychotics can modulate NMDA activity, and this effect can contribute to their clinical efficacy (Choi et al., 2009). Taken together, this evidence suggests that alterations in dopamine and glutamate signaling can alter dFC and contribute to the pathophysiology of SCZ and BD.

6.4.5. Limitations

First, there was considerable heterogeneity in the image acquisition parameters and dFC techniques used by the included studies. Second, the characteristics of the patients differed between the studies, increasing the ecological validity of this study, but, at the same time, contributing to the heterogeneity of our findings. Third, the majority of patients were medicated, which could have influenced our results.

6.5. Conclusions

A pattern of abnormal dFC was observed in SCZ, involving EXE, SAL and DMN, and these alterations were associated with psychopathological features such as hallucinations and delusions. In BD, a mixed picture of altered dFC was observed, with only some studies reporting an association with affective symptoms. Overall, the study of dFC is extremely complex, as the time scale of the phenomena that occur in the brain can be highly variable, the number of states is unknown, and they can be intertwined and interact with each other. Furthermore, cross-frequency coupling may drive the self-organized dynamics of brain states with low-frequency oscillations modulating the synchronization patterns of faster rhythms (Vanhatalo et al., 2004). Recent approaches have tried to unravel the interaction between brain states and have considered the coexistence of multiple states at a specific time point rather than an all-or-nothing phenomenon (Miller et al., 2016b). These achievements have contributed to a better understanding of SCZ and BD in terms of brain dynamics. Future studies on the physiology, reliability and replicability of dFC indexes are needed to create gold standard measures for this novel field, thus allowing the comparability across studies, and more thorough analyses of the molecular and electrophysiological correlates of these phenomena (Hutchison et al., 2013).

7. STUDY 6: SPONTANEOUS BRAIN ACTIVITY AND LOCAL CONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

7.1. Introduction

As previously reported, SCZ and BD present a significant overlap in risk genes and clinical features (Lichtenstein et al., 2009; Murray et al., 2004). In SCZ, rs-fMRI investigations have shown FC abnormalities within the PFC and between cortical and subcortical regions, whereas, at a network level, alterations were mainly found in the DMN, SAL, EXE and SM (Karbasforoushan and Woodward, 2013; Manoliu et al., 2014; Tang et al., 2012; Wang et al., 2017). In BD, FC alterations have been reported mostly in the amygdala, cingulate cortex and PFC (Syan et al., 2018). Additionally, a recent systematic review by our research group reported that both SCZ and BD patients present abnormalities in dynamic interplay between the DMN, SAL and EXE (Cattarinussi et al., 2023a). To the best of our knowledge, only few studies on ALFF, fALFF and ReHo have been conducted in SCZ and BD, and no investigation has directly compared spontaneous brain activity and local connectivity in the two patient groups. In this context, we decided to explore changes in resting-state brain activity in a sample of SCZ and BD patients HC. Our work had two main objectives: first, to further the knowledge about the shared and distinct resting-state alterations of SCZ and BD; second, to evaluate the association between resting-state features and clinical symptoms and cognitive functioning in SCZ and BD. Based on previous literature, we hypothesized to find spontaneous brain abnormalities in those areas implicated in the pathophysiology of the disorders, including prefrontal, striatal, thalamic and limbic areas. We also speculated that the clinical symptoms and cognitive deficits in SCZ and BD could be associated with abnormal brain activity.

7.2. Methods

7.2.1. Participants

Patients with SCZ, BD and HC were selected from the Consortium for Neuropsychiatric Phenomics dataset (https://openneuro.org/datasets/ds000030/versions/00016). The dataset contains data of 272 participants, aged 21-50, who completed a minimum of eight years of formal education. Subjects were recruited via community advertisement, local clinics and online portals and completed a comprehensive neuropsychological battery, in addition to the MRI scan. Exclusion criteria for the three groups were: a) left-handedness; b) history of severe head injury with loss of consciousness; c) contraindications to MRI. Moreover, HC were excluded if they presented a lifetime or current diagnosis of any psychiatric disorder. From the initial sample, we decided to exclude individuals with mild head injury that resulted in loss of consciousness between 2 and 30 minutes, current medical illness, past or current substance use disorder, history of attention hyperactivity disorder, anxiety disorders and major depressive disorder. Three subjects did not complete the rs-fMRI acquisition and ten were excluded for excessive head-motion (see below). The final sample included 40 patients with SCZ, 43 patients with BD type I in partial or full remission and 59 HC.

7.2.2. Clinical and cognitive assessment

Current and lifetime diagnoses were obtained with the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID) (DSM-IV). Psychopathological evaluation was carried out using the HAM-D (Hamilton, 1960), the SANS (Andersen, 1989), the SAPS (Andersen, 1984) and the YMRS (Young et al., 1978). Cognitive abilities were assessed with the Wechsler memory scale, California Verbal Learning test, Stroop test, Attentional network task, Continuous performance test, Task Switch task and Stop Signal task.

7.2.3. Imaging acquisition

Neuroimaging data were acquired on a 3 Tesla Siemens Trio scanner. A T1-weighted high-resolution anatomical scan (MPRAGE) was collected with the following parameter: slice thickness = 1 mm, 176 slices, TR = 1.9 s, TE = 2.26 ms, matrix = 256 x 256, FOV = 250 mm, sagittal plane, slice thickness = 1 mm, 176 slices. Functional MRI data were collected with a T2*-weighted echoplanar imaging (EPI) sequence with the following parameters: slice thickness = 4 mm, 34 slices, TR = 2 s, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, FOV = 192 mm, oblique slice orientation. The resting-state fMRI scan lasted 304 s. Participants were asked to remain still with their eyes open.

7.2.4. Preprocessing

Structural and functional magnetic resonance imaging data were pre-processed using DPABI and SPM12, running under the MATLAB R2022a (The Mathworks, Sherborn, MA, USA). Briefly, all the images were inspected for anatomical abnormalities or artefacts by expert neuroscientists. Then, images were reoriented and realigned for head motion correction. After this, T1-weighted images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). GM images were then normalized to the MNI space using DARTEL registration with a resulting isotropic voxel size of 3 mm x 3 mm x3 mm. A total of 10 subjects were excluded for excessive head motion.

7.2.5. Static spontaneous brain activity and local connectivity

To test the spontaneous brain activity and local connectivity differences between SCZ, BD and HC we explored fALFF and ReHo using DPABI. We decided to explore fALFF since it is a normalized index of ALFF that can provide a more specific measure of low-frequency oscillations (Zuo et al., 2010). For fALFF analyses, the filtered time series of each voxel was transformed into the frequency domain with a Fast Fourier Transform and the power spectrum was obtained. First, we measured ALFF by calculating the square root of the signal across 0.01–0.08 Hz for each voxel (Zang et al., 2007). For fALFF measurement, the sum of the amplitude values in the 0.01 to 0.08 Hz low-frequency

power range was divided by the sum of the amplitudes over the entire detectable power spectrum (range: 0.01–0.1 Hz). The fALFF value for each voxel was z-normalized across the full brain for each subject for standardization purposes. For ReHo, KCC was assigned to a given voxel by calculating the KCC of times series of the voxel and the nearest 26 voxels (Zang et al., 2004). Higher ReHo values of a given voxel represent a higher degree of localized temporal synchronization within a neighboring cluster. Then, the ReHo value for each voxel was z-normalized across the full brain for each subject to guarantee the standardization. fALFF and ReHo maps were smoothed with a Gaussian kernel of 4-mm full width at half maximum.

7.2.6. Statistical analyses

Demographics and clinical data were compared using ANOVA, two-sample t-test and χ^2 test as appropriate. Normality of the data was tested with the Shapiro Wilk test. Group differences in fALFF and ReHo among three groups were identified with voxel-based one-way ANOVA in SPM12. Conjunction analyses were performed to identify areas of overlap between SCZ and BD (SCZ > HC and BD > HC; SCZ < HC and BD < HC). Voxel-wise threshold was set at $p < 0.001$ with FWE cluster-level correction $\alpha = 0.05$. Then, szfALFF and szReHo values were acquired from abnormal regions in three groups for post-hoc analysis. An exploratory factor analysis was conducted on cognitive scores to reduce data to a smaller set of summary variables. Neuropsychological Factors were rotated with an oblique Promax rotation (FDR $\alpha = 0.05$). Spearman correlation analyses were used to assess the relationship between fALFF and ReHo values and clinical and cognitive scores. Statistical analyses were conducted with Jamovi (2.0.0.0).

7.3. Results

7.3.1. Demographic and cognitive data

The sample included 40 SCZ (mean age = 37.5 ± 8.6 years, 31 M), 43 BD type I (mean age = 35.1 ± 8.9 years, 26 M) and 59 HC (mean age = 33.1 ± 8.8 years, 32 M). No differences in age (F=1.29,

p=0.28) and sex (χ^2=5.64, p=0.06) were observed between the groups. SCZ presented higher SANS and SAPS scores compared to BD (p<0.001), but no differences were observed in HAM-D or YMRS between the two groups (see Tab. 1 in the Appendix). The exploratory factor analysis resulted in 3 factors exploring memory (factor 1), verbal learning and working memory (WM) (factor 2) and inhibition (factor 3). SCZ had worse memory (PC1), verbal learning and WM (PC2) and higher inhibition (PC3) scores compared to BD and HC (all p's < 0.001), while BD presented lower memory (PC1) and verbal learning and WM (PC2) scores and higher inhibition (PC3) scores compared HC (all p's < 0.046).

7.3.2. Group differences in fALFF

SCZ vs. HC. We found a decrease in fALFF in SCZ compared to HC in the left middle frontal gyrus (MFG), right precentral gyrus, bilateral postcentral gyrus, bilateral superior parietal lobule (SPL), left supramarginal gyrus, left inferior occipital gyrus (IOG) and left cuneus. Conversely, SCZ presented an increase in fALFF in the right posterior cingulate cortex (PCC), left inferior temporal gyrus (ITG) right posterior insula, left caudate and right cerebellum compared to HC (Fig. 30a).

BD vs. HC. BD showed lower fALFF compared to HC in the right middle postcentral gyrus, right IOG and right occipital fusiform gyrus and higher fALFF in the bilateral MFG, right precentral gyrus, left transversal gyrus, right caudate and left thalamus (Fig. 30b).

SCZ and BD vs. HC. Both SCZ and BD showed higher fALFF in the right precentral gyrus relative to HC (Fig. 30c).

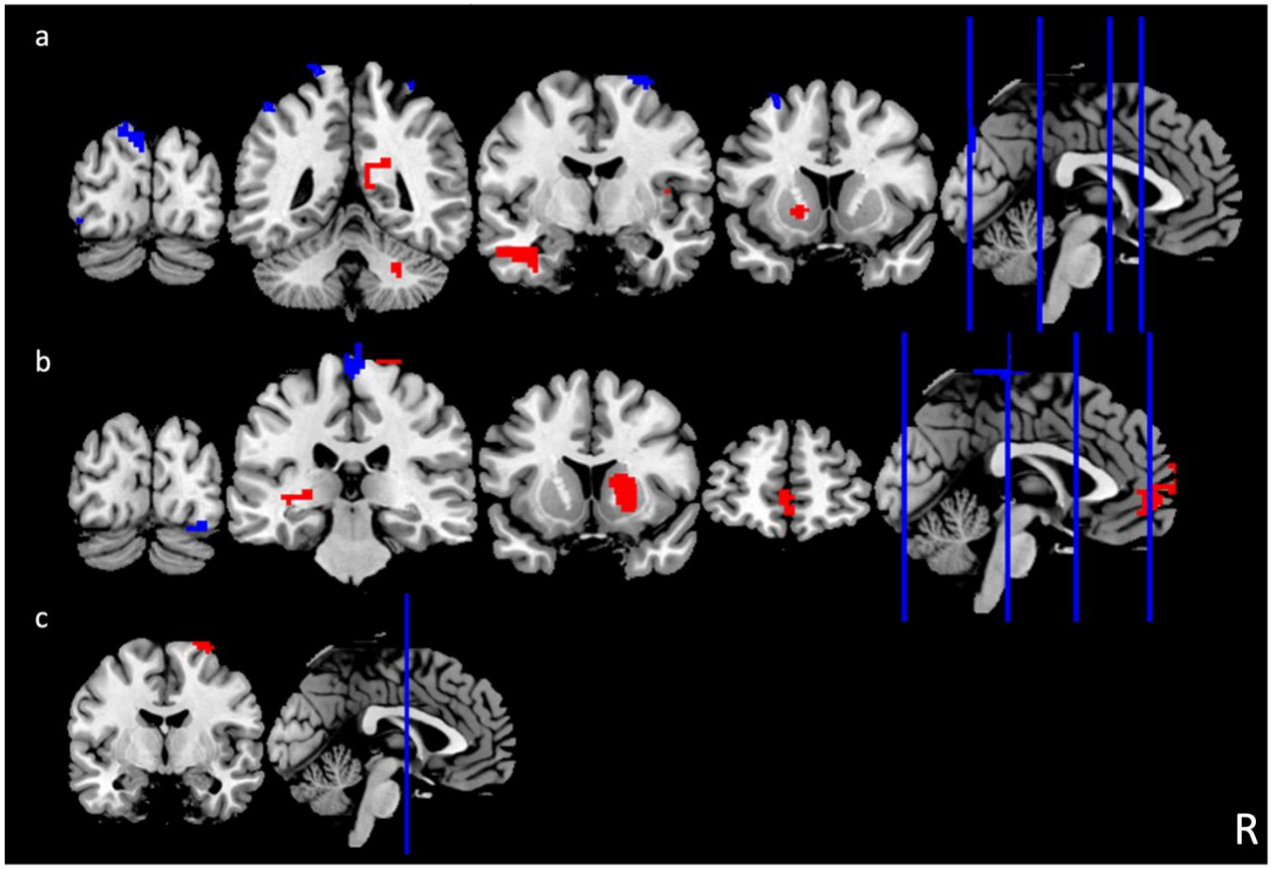

Figure 30. Group differences in spontaneous brain activity in individuals with SCZ and BD. Fig a) Brain areas with altered fALFF in SCZ compared to HC; Fig. b) Brain areas with altered fALFF in BD compared to HC; Fig. c) Brain areas with altered fALFF in SCZ and BD compared to HC. Significance level was set at false discovery rate corrected $p < 0.05$. Blue and red denote increased and decreased fALFF values, respectively. R = right.

7.3.3. Group differences in ReHo

SCZ vs. HC. ReHo values were decreased in SCZ compared to HC in the bilateral IOG and right postcentral gyrus, while they were increased in the right anterior orbital gyrus, left posterior orbital gyrus, bilateral temporal pole, right hippocampus and left cerebellum (Fig. 31a).

BD vs. HC. In BD there was a decrease in ReHo compared to HC in the right middle temporal gyrus (MTG) and left PCC and an increase in the right MFG, right STG and left anterior insula (Fig. 31b).

SCZ vs. BD. SCZ presented lower ReHo compared to BD in the right calcarine scissure (Fig. 31c).

SCZ and BD vs. HC. SCZ and BD showed lower ReHo in the right IOG compared to HC (Fig. 31d).

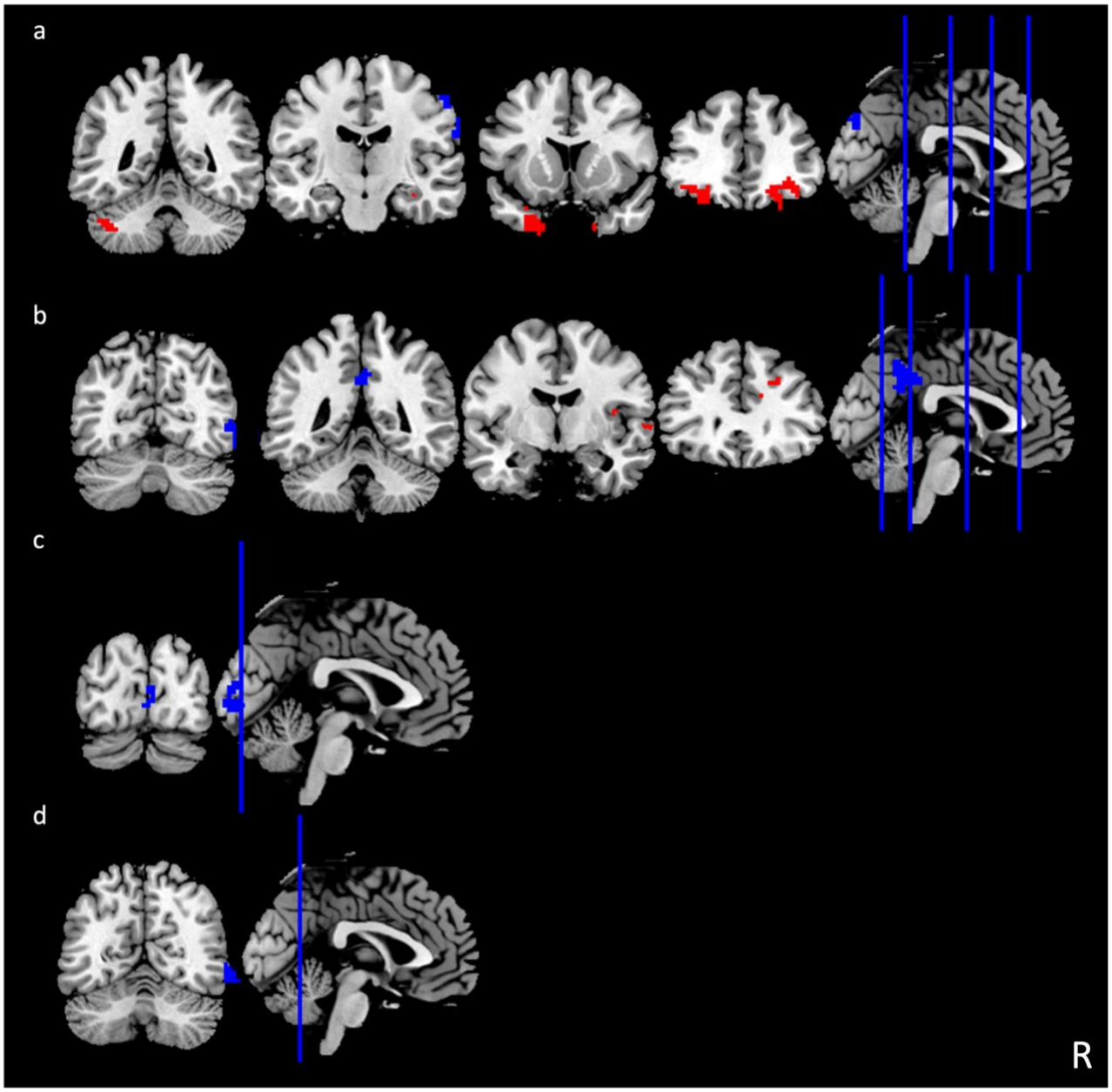

Figure 31. Group differences in local connectivity in individuals with SCZ and BD. Fig. a) Brain areas with altered ReHo in SCZ compared to HC; Fig. b) Brain areas with altered ReHo in BD compared to HC; Fig. c) Brain areas with altered ReHo in SCZ compared to BD; Fig. d) Brain areas with altered ReHo in SCZ and BD compared to HC. Significance level was set at false discovery rate corrected $p < 0.05$. Blue and red denote increased and decreased ReHo values, respectively. R = right.

7.3.4. Association between abnormal fALFF and ReHo and clinical metrics

Exploratory analyses showed that, in SCZ, ReHo values of the left temporal pole were negatively correlated with PC1 (rho=-0.350 p=0.037), fALFF values of the left cuneus were positively correlated with PC2 (rho=-0.381 p=0.022) (r=0.35 p=0.02) and fALFF and ReHo values of the right postcentral gyrus were positively correlated with the SAPS scores (rho=0.328 p=0.039; rho=0.322 p=0.043,

respectively. In BD, PC1 were negatively correlated with the fALFF values of the left transversal temporal gyrus (rho=-0.316 p=0.04), right caudate (rho=-0.336 p=0.028) and right precentral gyrus (rho=-0.411 p=0.007), as well as with ReHo values of the right anterior insula (rho=-0.399 p=0.008), right MFG (rho=-0.390 p=0.01) and right STG (rho=-0.364 p=0.016). PC2 were negatively correlated with the fALFF values of the left MFG (rho=-0.331 p=0.031), left thalamus (rho=-0.312 p=0.042), left transversal temporal gyrus (rho=-0.361 p=0.018), right caudate (rho=-0.359 p=0.018), right MFG (rho=-0.315 p=0.040), right precentral gyrus (rho=-0.421 p=0.005) and ReHo values of the right anterior insula (rho=-0.407 p=0.007), right MFG (rho=-0.355 p=0.019) and right STG (rho=-0.379 p=0.012). PC3 were positively correlated with the ReHo values of the right STG (rho=-0.303 p=0.048).

7.4. Discussion

In this study, we explored intrinsic neural activity in SCZ and BD and we conducted exploratory analyses to test the association between FC metrics clinical and cognitive features in these patients. The results showed widespread spontaneous brain activity and local connectivity alterations in patients, involving cortical and subcortical areas and the cerebellum. SCZ and BD were characterized by dysconnectivity in the prefronto-striatal circuit, in addition to alterations in the visual cortex.

In the following sections we will first discuss the fALFF and ReHo alterations between the three groups and their association with clinical and cognitive symptoms.

7.4.1. fALFF abnormalities in SCZ and BD

Widespread fALFF abnormalities were observed in SCZ and BD. In SCZ, these alterations were located in the frontal, parietal, temporal and occipital cortex, as well as in the insula, striatum and cerebellum. Differently, fALFF alterations in BD were observed in the prefrontal, parietal, temporal, occipital, striatal and thalamic areas. Interestingly, both SCZ and BD showed higher fALFF in the right precentral gyrus compared to HC. In line with previous findings by our research group on

individuals with first episode psychosis (FEP) (Cattarinussi et al., 2023b), SCZ and BD presented spontaneous activity alterations in the fronto-striatal circuit. Crucially, dysconnectivity in the prefronto-striatal circuit is highly implicated in the pathophysiology of psychosis (Weinberger, 1987). Indeed, a large body of research has highlighted the presence of transdiagnostic fronto-striatal dysconnectivity in both SCZ and BD with or without psychotic symptoms (Karcher et al., 2019; Okanda Nyatega et al., 2022). Notably, fronto-striatal changes have also been reported in individuals at genetic (Cattarinussi et al., 2022) and clinical risk for psychosis (Fusar-Poli et al., 2010) both at rest and during the performance of a task, suggesting that abnormalities at this level might represent both a phenotype of risk and a biomarker of the disorders. Furthermore, the findings of fronto-striatal alterations across the psychosis spectrum, spanning from individuals at risk to patients with a recent onset of the symptoms to chronic medicated patients, indicates that fronto-striatal dysfunctions are not associated with antipsychotic treatment but represent an intrinsic marker of psychotic disorders. Interestingly, in BD, fronto-striatal alterations were linked to deficits in memory, verbal learning and WM, indicating a potential role of fronto-striatal dysconnectivity in cognitive functioning in these patients. Somewhat surprisingly, these correlations were not observed in SCZ. It is noteworthy though that, due to the high number of variables, we could only perform exploratory analysis, therefore the results need to be interpreted with caution.

7.4.2. ReHo abnormalities in SCZ and BD

Similarly to fALFF, also ReHo analyses revealed widespread cortical and subcortical local connectivity changes, mostly in the prefrontal, parietal, temporal, occipital, hippocampal and cerebellar regions in SCZ and in fronto-temporal areas, posterior cingulate and insula in BD. The direct comparison of SCZ and BD showed a decrease ReHo in SCZ compared to BD in the right calcarine scissure, while both SCZ and BD presented lower ReHo in the right IOG compared to HC. The visual system plays a key role in the pathology of psychotic disorders. Several studies have reported impairments at multiple levels of visual processing, ranging from perceptual integration to

speed discrimination and higher-order visual functions, which are associated with positive and negative psychotic symptoms (Türközer et al., 2022). In addition, it has been shown that early visual processing deficits may affect higher-order cognitive functions, including emotion recognition, via bottom-up mechanisms (Butler et al., 2009). Interestingly, visual impairments in childhood and adolescence are linked to development of SCZ later in life (Hayes et al., 2019). Also, visual impairments have been reported in first-degree relatives of individuals with psychosis (Calkins et al., 2008; Chen et al., 1999), suggesting that visual system deficits might be implicated in the pathophysiology of psychosis. In line with this evidence, we observed that both individuals with SCZ and BD presented a decrease in ReHo in the IOG, a region structurally connected with the limbic system with a central role in face and emotion processing (Sato et al., 2017; Xiu et al., 2015). Additionally, SCZ specifically presented a reduction in ReHo in the right calcarine scissure, an area that plays a central role in reality-monitoring, defined as the process that allows us to distinguishing imagination and thoughts from information we perceive from the environment (Lavallé et al., 2023). This evidence aligns with core psychopathological features of the two disorders and suggest that both SCZ and BD present changes in areas involved in affective processing, while only SCZ shows alterations in brain regions implicated in reality-monitoring, which might be associated with delusions and hallucinations.

7.4.3. Limitations

First, the small sample size may have affected our results. Second, we did not have information about the medications that the patients were taking, so we cannot make inferences on the role of medications on resting-state metrics in our sample. Third, illness-related factors, including the chronicity of the illness itself, cigarette smoking and substance abuse, may have affected our findings. Also in this case, no information about duration of the illness of comorbidities was available. Lastly, the cross-sectional design limits our ability to make inferences or causation regarding the neurobiological features underlying SCZ-BD spectrum disorders.

7.5. Conclusions

In conclusion, we provided evidence of widespread aberrancies of spontaneous activity and local connectivity in SCZ and BD. SCZ and BD were characterized by dysconnectivity in the prefronto-striatal circuit, as well as alterations in the visual cortex subserving face and emotion processing and reality-monitoring. Future investigations and longitudinal research design that follow up patients during the course of the disorders will allow to broad our understanding of the pathophysiology of these findings.

CHAPTER 5: GENERAL DISCUSSION

In the last decades, the study of task-based and resting-state properties of the brain in individuals with psychosis has played a key role in further our understanding on the pathophysiology of the schizophrenia – bipolar disorder spectrum.

The main goal of this project was the characterization of brain alterations in the schizophrenia – bipolar disorder spectrum, spanning from the risk to the chronic disorders. To do so, we investigated MRI and fMRI changes in unaffected REL of individuals with SCZ and BD, who do not present the clinical manifestations but show some of the brain abnormalities that are associated with the disorders. Secondly, we explored functional brain metrics in individuals within the first five years of symptoms onset in order to share a light on the neural correlates of psychosis in the absence of the confounding factors related to the chronicity of the illnesses. In this population we also examined how inflammation, a key risk factor in the development of psychiatric disorders, affected brain function. Lastly, we focused on individuals with SCZ and BD, to explore the shared and distinct brain functional alterations of the two disorders and to clarify their role in the development of psychotic and affective symptoms.

The following main results emerged. First, the familial risk for SCZ was associated with alterations in cortico-striatal-thalamic loop, spanning across the DLPFC and temporal regions, while the genetic risk for BD was linked to abnormalities in thalamo-cortical and limbic regions, including the VLPFC, superior parietal and medial temporal cortices. Furthermore, the thalamus emerged as a common area associated with the risk for both disorders. Changes in the prefronto-striatal circuit were also observed in individuals with FEP within five years from symptoms onset, irrespectively of medication status. In this population we also observed a general impairment of the dynamics of the brain, not only at the level of specific states, but also at a global level with reduced overall brain dynamics. Crucially, when we explored the potential effect on brain metrics of inflammation, which is considered a major risk factor for the development of psychiatric symptoms, we observed that low levels of inflammation

were positively correlated with spontaneous activity in the SFG and cerebellum, while they were negatively correlated with the spontaneous activity in the postcentral and precentral gyri. The picture in chronic disorders is more heterogeneous and affected by several confounding factors, including the neuromodulatory effects of drugs. With regards to brain dynamics, we found a dysfunction of the triple network involved in goal-directed behaviors and of the sensory-motor networks both in SCZ and BD. Dynamic functional alterations were more marked in SCZ compared to BD and presented a clear association with psychotic symptoms. Lastly, we observed that SCZ and BD were characterized by dysconnectivity in the prefronto-striatal circuit, which may be the expression of the shared genetic and environmental mechanisms underlying both disorders. Furthermore, the involvement of different nodes of the visual cortex may be associated with a differential symptom expression in the two disorders.

Prefrontal inefficiency during working memory tasks is a well-characterized IP for SCZ (Blokland et al., 2011; Callicott et al., 2003a) and a marker of the disorder (Eryilmaz et al., 2016; Manoach et al., 1999) that results in altered processing and maintaining the information in the working memory system (Callicott et al., 2003b). Recent advancements in genetic studies have demonstrated that prefrontal inefficiency during working memory paradigms is associated with PRS for SCZ, a measure indicating the cumulative risk for a disorder by aggregating the effects of SNP (Walton et al., 2014). Aberrant prefrontal function is not a unique feature of SCZ, but it has also been related to BD (Blumberg et al., 1999; Cattarinussi et al., 2019; McIntosh et al., 2008). In our studies, prefrontal abnormalities were observed at every stage of the schizophrenia – bipolar disorder spectrum. In particular, in SCZ-REL, the risk for SCZ was associated with an increased activity and volumetric changes in the DLFPC, an area that approximately corresponds to BA9 and BA46 and consists of the lateral part of SFG and MFG (Petrides and Pandya, 1999). The DLPFC is implicated in higher cognitive processes, including working memory, cognitive control, planning and response inhibition, and plays a central role into the pathophysiology of the disorder (Becker et al., 2008; Blasi et al., 2006; Conklin et al., 2000; Smucny et al., 2021; R. Zhang et al., 2016). In SCZ-REL, the DLPFC

hyperactivation is considered a compensatory mechanism consisting of higher recruitment of prefrontal resources to successfully perform a cognitive task (Seidman et al., 2006). Differently, BD risk was associated with VLPFC alterations, which might underlie deficits in cognitive control, emotional regulation and impulsivity (Adler et al., 2005). Evidence from FEP studies showed prefrontal abnormalities located in the DLPFC and in the adjacent SFG. In this population, we were also able to demonstrate an association between inflammation levels and abnormalities in the SFG, suggesting that prefrontal abnormalities might not only be related to genetic mechanisms but also to environmental factors.

One of the most consistent results from GWAS of SCZ is a significant association between the disorder and genetic variation in the major histocompatibility region of chromosome 6 (Ripke et al., 2014; Stefansson et al., 2009), which encodes molecules involved in inflammation and immunity (Sekar et al., 2016). Additionally, a strong association between SCZ and the complement system gene C4 was found in a GWAS of more than 28.000 SCZ cases and 35.000 control cases (Sekar et al., 2016). Notably, post-mortem studies have showed evidence of immune activation in the DLPFC in up to 50% of individuals with SCZ compared to a significantly smaller percentage (~0–10%) of age-matched non-schizophrenic controls (Volk et al., 2019, 2015). Considering that DLPFC abnormalities are hallmarks of SCZ, it has been proposed that inflammation in this region drives neuropathology in a group of patients. Indeed, patients with SCZ displaying high neuroinflammation levels tend to present worse psychotic symptoms (Jacomb et al., 2018), reduced verbal fluency (Fillman et al., 2016) and prefrontal grey matter volume reductions (Y. Zhang et al., 2016) compared to patients with normal levels of inflammatory markers. Furthermore, at the clinical level, elevations in inflammatory markers including the acute phase CRP and pro-inflammatory cytokines have been found in the serum of individuals with SCZ (Chase et al., 2016; Di Nicola et al., 2013), although some conflicting results have been reported (Haack et al., 1999). Taken together, this evidence supports the notion that a significant percentage of individuals with SCZ present higher inflammation, and that altered pro-inflammatory processes influence prefrontal structure and function. In sum, the prefrontal alterations

that we observed in unaffected REL and in FEP might be to the one hand due to genetic vulnerability mechanisms, and to the other to inflammatory processes. We speculate that, at least in some patients, inflammation might represent the biological mechanisms that underlie prefrontal inefficiency in psychosis.

In our study, prefrontal inefficiency was also observed in individuals with SCZ and BD. Although we did not directly compare the magnitude of prefrontal changes between the early phases of the disorder and the chronic phases, it has been previously demonstrated that in SCZ and BD, prefrontal abnormalities worsen with illness progression (Abé et al., 2023; Kani et al., 2017). This result is in line with studies exploring cognition in SCZ and BD patients, which showed a progressive decline in cognitive functions, in particular on those that rely most on the PFC (Keefe, 2014; Macoveanu et al., 2021).

In sum we can conclude that prefrontal inefficiency appears in individuals at risk for psychosis and persists during the course of the disorder. Prefrontal alterations, in particular involving the DLPFC, could be influenced by the inflammation status and do not seem to be affected by anti-inflammatory medications.

Another consistent finding of our studies was the presence of striatal abnormalities, that, similarly to prefrontal alterations, were observed throughout the psychosis course. Importantly, striatal changes were observed not only in studies examining static FC, but also in investigations exploring the temporal dynamics of the fMRI signal. The striatum, along with the globus pallidus, forms the basal ganglia, a group of subcortical nuclei embedded deep in the brain primarily responsible for motor control, motor learning, executive functions and emotions (Lanciego et al., 2012). The ventral part of the striatum is involved in reward anticipation (Bhanji and Delgado, 2014). Importantly, recent neuropsychological investigations have demonstrated that individuals at genetic risk for SCZ exhibit deficits in reward learning abilities (Hanssen et al., 2020). Similarly, in SCZ, investigations employing reward tasks, have shown abnormalities in ventral striatum activation, which appear to be linked to a difficulty in differentiating between expected and unexpected feedback and lead to an

overvaluation of the outcome (Arrondo et al., 2015; Morris et al., 2012; Tikàsz et al., 2019). With regards to FEP, a recent fMRI study comparing individuals with high schizotypal-personality traits, patients with non-affective FEP and HC, displayed ventral striatal hyperactivation in FEP, which correlated with the severity of psychotic symptoms (Kirschner et al., 2018). Differently, antipsychotic naïve patients showed reduced ventral striatal activation during reward anticipation (Esslinger et al., 2012), which has also been reported in individuals at clinical high-risk for psychosis (Rausch et al., 2015) and has been proposed as an IP for SCZ (Grimm et al., 2014). In addition, convincing evidence indicates the presence of significant reward learning deficit across BD subtypes compared to HC, and in particular a lower sensitivity to rewards compared to punishments both in BD type I and II (Pouchon et al., 2023). Similarly to SCZ, a recent meta-analysis has demonstrated the presence of altered activation in the striatum during reward tasks also in individuals with BD (Long et al., 2022). Since the reward circuit is altered through the psychosis spectrum (e.g., individuals at clinical and genetic risk, FEP, BD and SCZ), striatal abnormalities subjacent deficits in reward processes might represent a biomarker of psychosis. Differently from the ventral part, the dorsal striatum is mostly involved in sensorimotor function and impulsivity regulation, which appears to be altered in SCZ-REL (Kim and Im, 2019), as well as in BD-REL (Simonetti et al., 2021), FEP (Diaz et al., 2022), BD (Ramírez-Martín et al., 2020) and SCZ (Gong et al., 2023). Therefore, we suggest that dorsal striatal abnormalities might represent the neural correlates of impulsive behaviors across the psychosis spectrum. Crucially, we provided further evidence that striatal abnormalities are not only seen in medicated SCZ and BD patients, but also in SCZ-REL and antipsychotic-naïve FEP, suggesting that striatal alterations in the schizophrenia – bipolar disorder spectrum represent a stable marker of the disorder that is not primarily related to the use of antipsychotics.

Functional dysconnectivity of the fronto-striatal network has been long considered a key pathophysiological feature of acute and chronic psychosis (Howes et al., 2012; Schmitt et al., 2009). Crucially, a large body of research has demonstrated that fronto-striatal function is correlated with striatal dopamine receptor availability (Ghahremani et al., 2012) and synthesis capacity (Sabaroedin

et al., 2023). More recently, the glutamatergic hypothesis suggested that fronto-striatal dopamine abnormalities could derive from cortical glutamate alterations. In particular, it has been proposed that neurodevelopmental abnormalities could result in a hypofunction of NMDA receptors in cortical GABAergic parvalbumin-positive interneurons (Gonzalez-Burgos and Lewis, 2012). Consequently, the glutamate release from a cortico-cortical pyramidal neuron is unable to efficiently stimulate the GABAergic neurons, which in turn fail to inhibit downstream cortico-brainstem pyramidal neurons, leading to excessive release of glutamate in the VTA and dopamine in the striatum (Howes et al., 2015). Glutamatergic excess has been frequently reported in SCZ, in particular in the prefronto-striatal circuit, and seems to be specific to the early stages of the disorder (Dempster et al., 2020; Egerton et al., 2018). Importantly, drug development efforts in SCZ have started to focus on ameliorating putative deficits in NMDA signaling (Yang et al., 2017), showing promising results. Interestingly, recent evidence has demonstrated that positive allosteric modulators of glutamate receptors influence fronto-striatal activity in SCZ (Wolf et al., 2022), providing novel insight into the potential role of fronto-striatal abnormalities as targets of new therapeutic mechanisms.

Overall, our results expanded on previous knowledge, showing that fronto-striatal dysfunctions are not only are present at distinct illness stages, but they also precede symptoms onset, and might be implicated in cognitive, emotion and reward control impairments. Crucially, fronto-striatal alterations might represent a promising biomarker for the development of new drugs with novel mechanisms of action.

Lastly, the picture in SCZ and BD was highly heterogeneous, with widespread functional abnormalities involving the cortex, subcortical areas and the cerebellum. The direct comparison of spontaneous brain activity in SCZ and BD showed that both groups were characterized by abnormalities in the IOG, a region involved in face and emotion processing, whereas only SCZ presented alterations in the calcarine scissure, which is implicated in the distinction between reality and internal processes. Importantly, sensory networks abnormalities in SCZ and BD were also reported by investigations exploring dFC, involving in particular the visual network. These results

align with core psychopathological features of the disorders and suggest that both SCZ and BD present changes in areas that play a role in affective processing, while only SCZ shows alterations in brain regions implicated in reality-monitoring, which might be associated with delusions and hallucinations.

Furthermore, in chronic patients we observed a consistent pattern of dFC alterations in the triple network. According to the triple network model, EXE, SAL and DMN interact in controlling higher cognitive and affective functions, with the EXE more active during cognitive and emotional tasks, the DMN showing the opposite activity pattern and the SAL mediating the interplay between the EXE and the DMN (Menon, 2011). Alterations of the triple network have frequently been reported both in SCZ and BD (Hare et al., 2019; Lee et al., 2018; Menon, 2019; Sambataro et al., 2021a; Whitfield-Gabrieli and Ford, 2012). Notably, recent evidence has described two neurobiologically distinct subtypes of SCZ based on triple-network patterns, accompanied by distinct deficits in sustained attention and cognitive flexibility (Liang et al., 2021). Additionally, a support vector machine study demonstrated that FC patterns of the triple network nodes were able to discriminate psychotic BD and SCZ (Palaniyappan et al., 2019), suggesting that the study of triple network FC could not only clarify the distinct pathophysiologic signatures of SCZ and BD, but could also identify discrete diagnostic/prognostic groups among individuals with psychosis. Overall, alterations within and between the EXE, SAL and DMN may underlie psychotic symptoms for deficits in salience attribution processes, affective symptoms for abnormal DMN persistence and cognitive impairments due to changes in the EXE. These alterations seem to be transdiagnostic across the schizophrenia – bipolar disorder spectrum, but they also present disorder-specific differences that may potentially have clinical utility and facilitate the discrimination between SCZ and BD. It is noteworthy that our dFC analysis revealed many FC alterations that were undetected by the static FC analysis, indicating that the study of dynamic patterns of brain activity might provide useful additional insight into the underpinnings of the schizophrenia – bipolar disorder spectrum.

Future directions

In the last decades, neuroimaging techniques have grown to become a promising additional tool for the diagnosis and detection of brain abnormalities associated with psychiatric disorders. However, the translational impact of these findings in clinical practice has been so far limited, as the commonly used univariate statistics did not properly deal with high-dimensional neuroimaging data. To overcome this limitation, machine learning (ML) techniques have started to be applied to neuroimaging data to identify patterns of structural and functional brain abnormalities that allow to differentiate individuals with psychiatric disorders from HC and to predict the illness course. Considering the value of ML in pattern recognition analyses, neuroimaging measures represent an ideal area of application of ML. Overall, ML might help us identifying neuroimaging markers with sufficient sensitivity and specificity that can predict outcomes at the individual level in FEP, SCZ and BD patients. This holds true also for individuals at familiar risk for SCZ or BD, where ML could be applied to develop multimodal prognostic workflow for an individualized prediction of transition to psychosis. In order to broaden our knowledge on the pathophysiology of the schizophrenia – bipolar disorder spectrum, genetic, neuroimaging, cognitive and clinical data need to be combined in large samples to identify multiple small effects that vary across individuals, ultimately enabling us to understand and predict the course of SCZ and BD at the level of the single subject and not only at group-level, thus facilitating early intervention strategies. Also, the use of ML techniques in large samples could help identifying valid and reproducible subgroups of psychotic patients characterized by qualitatively distinct inflammatory profiles. This might aid in understanding putative and separable mechanisms of illness and pathophysiologic processes in psychosis and may ultimately lead to the development of targeted intervention strategies.

Conclusions

These findings speak in favor of prefronto-striatal dysconnectivity as a key neurobiological feature in the pathophysiology of the schizophrenia - bipolar disorder spectrum. In particular, we observed

that changes in cortico-striatal-thalamic networks are associated with the risk for SCZ, while changes in cortico-thalamic and limbic regions are linked with the risk for BD. Individuals with manifest disorders present functional brain alterations that are mostly located in the prefronto-striatal circuit during the first phases of the disorder and tend to spread to cortical, subcortical and cerebellar regions with the illness progression. SCZ and BD present both overlapping and distinctive local and large-scale brain networks alterations, which can contribute to explain the similarities and the differences in the phenotypic presentations of the two disorders. At least in some psychotic patients, inflammation might represent the biological mechanisms that underlie prefrontal inefficiency.

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APPENDIX

STUDY 1: NEURAL CORRELATES OF THE RISK FOR SCHIZOPHRENIA AND BIPOLAR DISORDER: A META-ANALYSIS OF STRUCTURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

Table 1. fMRI studies of SCZ-REL: study characteristics.

Study (First author)	Year	Kinship with SCZ	Relatives			Healthy Controls			Quality score
			N	% F	age (ys) m (SD)	N	% F	age (ys) m (SD)	
Children									
Diwakar	2011	offspring	19	36.8	14.1 (2.9)	24	33.3	14.9 (2.8)	8.5
Hart	2013	1st degree (sib/off)	21	52	14.4 (2.6)	21	48	14.1 (2.6)	10
Keshavan	2002	offspring	4	50	13.3 (2.2)	4	50	12.5 (3.5)	8.5
Rajarethinam	2011	offspring	15	53.3	15.1 (3.4)	17	47.1	14.5 (3.5)	10
Adults									
Altamura	2012	siblings	18	33	33.3 (8.9)	24	23	30.4 (6.7)	10
Avsar	2011	1st degree	5	60	36.4 (15.4)	8	50	53.4 (15.4)	9
Becker	2008	1st degree (parents/sib/off)	17	64.7	33.3 (10.8)	17	41.2	32.7 (7.8)	8.5
Bonner-Jackson	2007	siblings	24	52.4	21.1 (3.5)	40	73.7	20.9 (3.5)	9.5
Brahmghatt	2006	siblings	18	61.1	20.7 (4)	72	52.8	20.3 (3.5)	10
Callicot	2003	siblings	23	73.9	34.4 (9)	18	38.9	29.6 (7)	10
Callicot	2003	siblings	25	56	36.6 (9)	15	60	27.9 (8)	10
Choi	2012	1st degree	17	47.1	20.7 (5.5)	16	43.8	21.4 (2.3)	9.5
Delawalla	2008	siblings	30	53.3	21.3 (3.5)	92	57.6	20.2 (3.4)	9.5
Deleeuw	2013	siblings	23	39.1	30.1 (4.2)	24	50	28.3 (5.4)	10
DeLeeuw	2015	siblings	27	48.1	31.7 (1.2)	29	58.6	30.3 (1.7)	10
Digiorgio	2013	siblings	48	50	36.3 (8.3)	53	52.8	35.6 (7.5)	10
Dodell-Feder	2014	1st degree	19	73.7	27.4 (3.9)	18	77.8	26.2 (4)	10
Filbey	2008	1st degree	6	66.7	53	8	37.5	41	7.5
Grimm	2015	1st degree (parents/sib/off)	54	57.4	33.6 (12.4)	80	51.3	33.5 (9.9)	10
Gromann	2014	1st degree	50	58	33.9 (8.7)	33	42.4	33.4 (10.2)	9.5
Hanssen	2015	siblings	94	56.4	36.4 (10.1)	57	44.9	32.2 (8.4)	8.5
Herold	2018	1st degree	12	50	42.9 (10.5)	12	58.3	37.0 (9.1)	10
Jiang	2015	parents	20	45	50.7 (5)	20	50	51.8 (5.9)	10
Karch	2009	1st degree	11	63.6	33.6 (8.8)	11	63.6	33.8 (9.2)	10
Landin-Romero	2014	siblings	28	39.3	36.8 (8.8)	56	32.1	36.6 (9.9)	9.5
Lee	2010	siblings	21	52.4	36.0 (10.3)	19	26.3	42.7 (9)	9
Li	2021	siblings	12	66.7	31.3 (8.2)	12	50	29.3 (7.2)	10
Li	2016	siblings	43	71	25.2 (3.1)	32	59	24.6 (2.8)	10
Li	2015	siblings	15	53.3	21.7 (6.1)	15	53.3	23.9 (5.2)	9
Liddle	2012	siblings	18	61.1	18.3 (2.2)	26	42.3	20.3 (4.9)	8
Lobianco	2012	siblings	23	65.2	33.9 (8.7)	24	41.7	31.9 (3.3)	10
Loeb	2017	siblings	30	43.3	19.4 (0.8)	39	46.2	20 (0.7)	10
LopezGarcia	2016	1st degree	16	43.8	57.0 (10.3)	20	60	32.7 (11.2)	9
Macdonald	2006	1st degree	21	67	33.2 (10.9)	20	50	33.4 (8.4)	8.5
Mcallidon	2010	1st degree	11	0	34.7	14	NR	36.4	8.5
Nook	2018	1st degree	21	66.7	27.3 (3.9)	19	73.7	26 (3.9)	9
Oertel	2019	1st degree	23	82.6	43.6 (14.3)	27	48.1	34 (11.4)	9
Park	2016	1st degree	20	65	23.9 (5.6)	17	52.9	23.1 (3.)	9.5
Pirnia	2015	1st degree	14	64.3	39.6 (11.8)	30	20	29.3 (9)	9
Pulkkinen	2015	offspring	51	60.1	22.4 (0.8)	52	61.5	22.3 (0.7)	10
Raemaekers	2006	siblings	16	50	33.9 (11.3)	16	50	33.4 (13.6)	9
Rasetti	2014	siblings	65	58.5	36 (1.2)	181	52.5	34.9 (0.7)	10
Sambataro	2013	siblings	65	63.1	36.6 (10.4)	235	51.9	31.8 (9.6)	10
Seidman	2006	1st degree	21	42.8	19.9 (4)	24	58.3	18.1 (3.3)	9.5
Seidman	2007	1st degree	12	58.3	34.8 (8.2)	13	53.8	36.9 (8.1)	9.5
Sepede	2010	siblings	11	54.5	34.4 (8.8)	11	54.5	32 (5.1)	10
Spilka	2015	1st degree	27	63	41.2 (25.5)	27	51.9	40.7 (11.1)	10
Spilka	2015	1st degree	27	63	41.2 (25.5)	27	51.9	40.7 (11.1)	10
Stablein	2018	1st degree	22	63.6	42.7 (14.9)	25	52	34.9 (10.5)	10

Stolz	2012	1st degree	16	62.5	23.0 (5.1)	28	67.9	26.9 (6.9)	9.5
Thermenos	2004	1st degree	12	66.7	35.5 (6)	12	50	32.2 (7.7)	10
Thermenos	2007	1st degree	21	42.9	19.9 (4)	26	62.5	18 (3.2)	9.5
Thermenos	2013	1st degree	43	71	25.2 (3.1)	32	59	24.6 (2.8)	10
Van Buuren	2011	siblings	24	66.7	29.4 (6.1)	25	72	27.5 (7.5)	10
VanderMer	2014	siblings	20	45	32.6 (8.6)	20	30	35.5 (11.7)	10
Venkatasubramanian	2010	siblings	17	17.6	25.2 (4.2)	16	12.5	24.4 (3.7)	10
Whyte	2006	1st or 2nd degree	41	56.1	26.6 (3.3)	21	38.1	26.8 (2.7)	10
Whitfield	2008	1st degree	13	23	22 (2.9)	13	38	20.5 (3.3)	9

SCZ: Patient with Schizophrenia; F: female; M: mean; SD: standard deviation; ys: years; NR: not reported. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 2. fMRI studies of BD-REL: study characteristics.

Study (First author)	Year	Kinship with BD	Relatives			Healthy Controls			Quality score
			N	% F	age (ys) m (SD)	N	% F	age (ys) m (SD)	
Children									
Chang	2017	offspring (BD I or II)	50	42	13.5 (2.9)	29	48	13.6 (2.8)	10
Kim	2012	1st degree (off or sib) (BD I or II)	13	54	13.9 (2)	21	48	13.7 (1.9)	9.5
Manelis	2015	offspring	29	41.1	13.81 (2.45)	23	47.9	13.74 (1.8)	9.5
Manelis	2016	offspring	29	41.1	13.81 (2.45)	23	47.9	13.74 (1.8)	9
Olsavsky	2012	1st degree (off and/or sib)	13	46	14 (2.4)	56	14	14 (2.6)	9.5
Pagliaccio	2017	1st degree (off or sib) (BD I or II)	29	48.3	14.9 (3.5)	53	60.4	18.7 (4.1)	10
Thermenos	2011	1st degree (psy)	10	50	18.4 (4.2)	10	50	17.1 (1.4)	8.5
Tseng	2015	1st degree (off or sib)	13	38.5	13.7 (2.3)	37	56.8	14.7 (2.3)	10
Wiggins	2016	1st degree	22	41	15.7 (3.6)	41	49	17.3 (4.2)	10
Adults									
Allin	2010	1st degree (BD I)	19	42	40.5 (13.9)	19	47.3	39.9 (11)	10
Alonso-Lana	2016	Siblings (BD I or II)	20	80	43.8 (11.1)	40	72.5	42.4 (10.7)	9.5
Chan	2016	1st or 2nd degree (BD I)	43	44.2	23.8 (2.5)	54	61.1	23 (2.4)	10
Drapier	2007	1st degree (parents/sib/off) (BD I)	20	40	43 (13.8)	20	50	41.9 (11.6)	9
Frangou	2011	1st degree (off or sib) (BD I)	48	50	36.5 (13.8)	71	49.3	39.8 (15.3)	9
Kanske	2015	1st degree (parents/sib/off) (BD I)	17	47	36.7 (16.3)	17	47	35.94 (15.63)	9.5
Linke	2012	1st degree (BD I)	22	50	45 (10)	22	50	28 (11)	9.5
Pompei	2011	1st degree (off or sib) (BD I)	25	48	35 (13.7)	48	48	36.3 (12.8)	9
Roberts	2013	1st degree (BD I or II) (off or sib)	47	53.2	24.6 (3.8)	49	65.3	23.2 (3.4)	9.5
Sepede	2012	1st degree (BD I)	22	68.2	31.5 (7.3)	24	66.7	32.5 (6.2)	9.5
Sugihara	2016	MZ twins	28	78.5	40.6 (14.5)	96	79.1	35.6 (11.4)	9.5
Surguladze	2010	1st degree (BD I)	20	40	43 (13.8)	20	50	41.9 (11.6)	9.5
Thermenos	2010	1st degree	18	55.6	36.3 (2.6)	19	52.3	39.2 (2.7)	9.5

BD: Patient with Bipolar Disorder; F: female; M: mean; SD: standard deviation; ys: years. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 3. VBM studies of SCZ-REL: study characteristics.

Study (First author)	Year	Kinship with SCZ	Relatives			Healthy Controls			Quality score
			N	% F	age (ys)	N	% F	age(ys)	
Children									
Sugranyes	2015	offspring	38	34.2	11 (3.3)	83	53	12.4 (3.1)	10
Wagshal	2015	siblings	14	42.9	12.1 (2.4)	46	45.7	12.9 (2.6)	8.5
Adults									
Chang	2016	offspring	31	32.3	18.4 (3.4)	71	62	20.6 (3.5)	10
Guo	2014	siblings	20	30	23.3 (3.4)	43	41.9	23.7 (2.8)	10
Guo	2014	siblings	25	32	23 (4.5)	43	41.9	23.7 (2.8)	10
Guo	2015	siblings	46	37	23 (4)	46	50	23.3 (2.3)	10
Honea	2008	siblings	213	58.2	36.5 (9.8)	212	51.4	33.3 (9.9)	9
Hu	2013	siblings	45	35.6	22.6 (3.9)	59	35.6	23.2 (2.6)	10
Ivleva	2016	1st-degree	200	NA	NA	251	64.8	36.9 (12.1)	10
Job	2003	1st or 2nd degree	146	49.3	21.2 (2.9)	36	52.8	21.2 (3.4)	8.5
Li	2012	1st-degree (sib/off)	21	66.7	21.1 (5.5)	48	50	22 (5.1)	9.5
Lui1a	2009	parents	10	70	41.4 (3.7)	10	60	43.2 (6.3)	10
Marcelis	2003	1st-degree	32	56.3	35.5 (10)	27	55.6	35.5 (9.8)	9.5
Oertel-Knochel	2012	1st-degree	29	51.7	40.4 (15.9)	37	54.1	39.4 (10.5)	9.5
Tian	2011	parents	55	50.9	50.3 (5.1)	29	51.7	51.8 (5.6)	10

SCZ: Patient with Schizophrenia; M: mean; SD: standard deviation; ys: year. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 4. VBM studies of BD-REL: study characteristics.

Study (First author)	Year	Kinship with BD	Relatives			Healthy Controls			Quality score
			N	% F	age (ys)	N	% F	age(ys)	
Children									
Handford	2015	Offspring (BD I or II)	13	38	12.5 (3)	20	45	13.3 (2.5)	9.5
Ladouceur	2008	offspring (BD I or II)	20	55	13 (2.7)	22	68.2	14 (2.6)	9.5
Lin	2015	Offspring (BD I or II)	26	57.6	17.7 (5.4)	33	54.5	15.9 (4.4)	10
Adults									
Eker	2014	siblings (BD I)	28	42	34.9 (9.4)	30	67	34.7 (8.4)	8.5
Frangou	2011	1st-degree (off or sib) (BD I)	48	50	36.5 (13.8)	71	49.3	39.8 (15.3)	9
Hajek	2013	offspring (BD I)	30	66.7	19.5 (3.1)	31	64.5	20.6 (3.3)	8.5
Hajek	2013	offspring (BD I)	20	55	20.2 (4.2)	18	61.1	23 (3.5)	8.5
Kempton	2009	1st-degree (off or sib) (BD I)	50	52	33.8 (12.7)	52	48	35.2 (13)	8.5
Matsuo	2012	1st-degree	20	75	46.2 (10.7)	40	60	41.6 (9.1)	9.5
Sarıçiçek	2015	1st-degree (BD I)	25	54	32.1 (11)	29	72	33.6 (9.3)	8.5
Matsubara	2016	1st-degree (BD I or II)	10	50	54.8 (20.1)	27	62.9	48.3 (13)	9.5

BD: Patient with Bipolar Disorder; M: mean; SD: standard deviation; ys: year. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 5. Volumetric studies (ROI and/or whole brain volume) of SCZ-REL: study characteristics.

Study (First author)	Year	Kinship	Volume	Relatives			Healthy Controls			Quality score
				N	% F	age (ys)	N	% F	age (ys)	
Children										
Bhojraj	2011	offspring	Amy	23	47	15.4 (3.6)	27	58	16.6 (4.5)	10
Cullen	2008	1st or 2nd degree	Pit	22	50	13 (0.2)	32	53	13 (0.2)	9
De Zwarte	2018	offspring	Amy, cau, GM, hip, ICV, str, TBV, thal	40	70	13.7 (3)	40	47.5	12.7 (2.1)	10
Dougherty	2012	1st-degree	Amy, cau, str, TBV	26	58	14.5 (2.4)	43	58	14.2 (2.5)	9.5
Jou	2005	1st-degree (off or sib)	ICV	9	NA	NA	12	NA	NA	8
Kenshavan	1997	offspring	Amy, hippo	11	45.5	15.1 (2.7)	12	41.7	14.3 (5.4)	9.5
Kenshavan	2002	offspring	Amy, amy-hip ICV, TBV	17	52.9	15.6 (3)	22	50	14.6 (4.6)	10
Mattai	2012	siblings	Hip	78	50	14.9 (6)	79	35.4	14.9 (3.2)	9
Rajarethinam	2014	offspring	ICV, TBV	29	48.3	14.9 (3.4)	27	48.1	16.9 (5.7)	9
Shah	2015	1st-degree (off or sib)	Pit	38	53	16.6 (3.6)	40	65	16.6 (3.7)	9
Sismanlar	2010	offspring	Amy, Hip, thal	26	50	11.42 (2.2)	23	56.5	11.43 (2.1)	10
Sugranyes	2015	offspring	GM, ICV, TBV	38	34.2	11 (3.3)	83	53	11.8 (2.7)	9
Sugranyes	2017	offspring	GM	47	43.6	11.3 (0.5)	84	61.3	12.2 (0.4)	9
Van Haren	2019	offspring	GM, ICV, TBV	40	70	13.8 (3)	40	48	12.7 (2.1)	10
Adults										
Arnold	2014	1st-degree	Hip	74	75.7	40.7 (16.1)	145	53.8	38.4 (12.4)	10
Baarè	2001	MZ twins	Hip, ICV, TBV	15	40	35.1 (10.3)	15	40	35.6 (11.4)	9.5
Baarè	2001	DZ twins	Hip, ICV, TBV	14	42.9	35.7 (10.8)	14	42.9	35.1 (10.3)	9.5
Bois	2015	≥ 2 1st or 2nd degree	Hip	144	50	21.2 (3)	36	47.2	21.2 (2.4)	9
Boos	2011	siblings	GM, ICV, TBV	186	54.3	27.5 (6.8)	122	50	27.5 (8.2)	10
Brans	2008	siblings	GM, TBV	18	22.2	41.2 (8.8)	43	32.6	40.2 (8.2)	9
Cannon	1998	siblings	ICV	60	55	27.5 (6.8)	56	50	27.5 (8.2)	9
Chua	2000	1st degree	TBV	53	74	45.3 (14.9)	35	80	32.8 (10)	9
Collip	2013	siblings	Hip	37	62.2	28.3 (7.8)	32	68.8	31.7 (11.4)	9.5
De Zwarte	2018	MZ twins	Amy, cau, GM, hipm ICV, str, TBV, thal	13	38.5	33.6 (11)	169	55.6	32 (13.4)	10
De Zwarte	2018	DZ twins	Amy, cau, GM, hip, ICV, str, TBV, thal	18	27.8	38.5 (12.3)	169	55.6	32 (13.4)	10
De Zwarte	2018	MZ twins	Amy, cau, GM, hip, ICV, str, TBV, thal	7	42.8	40.5 (11.2)	15	40	29.2 (6.3)	9.5
De Zwarte	2018	DZ twins	Amy, cau, GM, hip, ICV, str, TBV, thal	7	42.8	36 (13.3)	15	40	29.2 (6.3)	9.5

De Zwarte	2018	siblings	Amy, cau, GM, hip, ICV, str, TBV, thal	201	52.7	27.7 (7.1)	167	50.3	27.7 (8.2)	10
De Zwarte	2018	parents	Amy, cau, GM, hip, ICV, str, TBV, thal	44	70.5	52.9 (4.3)	41	65.9	52.8 (4.6)	10
Ebner	2008	1st-degree	Hip, TBV	88	48.9	44.6 (15.6)	53	49.1	32.5 (12.9)	9.5
Ettinger	2010	MZ twins	Cau, TBV, thal	18	50	31.4 (11.2)	52	34.6	35.3 (10.1)	10
Francis	2013	≥ 1 1st + ≥ 1 2nd or 3rd degree	Hip, ICV	46	70	25 (3.1)	30	58	24 (2.9)	9
Frangou	2006	1st degree	TBV	55	56.4	46.3 (14.6)	39	48.8	33.4 (12)	10
Goghari	2010	1st-degree	Amy, hip, ICV	23	65	49.8 (6.5)	36	44	42.1 (11.4)	10
Gogtay	2003	siblings	GM, TBV	15	33.3	19.1 (6)	32	31.3	18.8 (6)	9
Habets	2012	siblings	Pit	37	62.2	28.3 (7.8)	32	68.8	32.9 (11.5)	9
Harms	2007	siblings	TBV, thal	25	60	22.3 (3.5)	40	45	21.2 (3.6)	9.5
Ho	2007	1st or 2nd degree	GM	46	56.5	19.9 (4.1)	46	56.5	20.9 (3.5)	10
Ho	2010	1st or 2nd degree	Hip	46	56.5	19.9 (4.1)	46	56.5	20.9 (3.5)	9.5
Honea	2008	siblings	GM	213	58.2	36.5 (9.8)	212	51.4	33.3 (9.9)	10
Hulshoff Pol	2012	twins	GM, ICV, TBV	26	46.2	37.4 (11.4)	164	56.1	37.6 (9.5)	9
Huslhoff Pol	2004	MZ twins	GM, ICV, TBV	11	45.5	39 (11.7)	11	45.5	37.4 (12.6)	10
Hulshoff Pol	2004	DZ twins	GM, ICV, TBV	11	54.5	34.6 (9)	11	54.5	32.6 (9.1)	10
Karmik	2013	siblings	Hip	31	NR	NR	49	NR	NR	8.5
Knochel	2016	1st-degree	Cau, thal	47	42.6	37.2 (11.1)	57	54.4	37.1 (9.2)	9.5
Lawrie	1999	≥ 2 1st or 2nd degree	Cau, str, TBV, thal	100	46	21.1 (2.8)	30	50	21.1 (2.3)	8.5
Lawrie	2001	≥ 2 1st or 2nd degree	Amy, amy-hip, cau, str, TBV, thal	147	49.7	21.2 (2.9)	36	52.8	21.2 (2.4)	9
Lei	2015	1st-degree	GM, TBV	42	45.2	43 (7.9)	40	45	42.5 (9.2)	10
Lei	2015	1st-degree	GM, TBV	25	52	44 (8.1)	40	45	42.5 (9.2)	10
Marcelis	2003	1st-degree	GM, TBV	32	56.3	35.5 (10)	27	55.6	35.5 (9.8)	9.5
McDonald	2002	parents	TBV	10	50	59.5 (7.5)	68	54.4	36.3 (11.2)	9.5
McDonald	2002	1st or 2nd degree familial	TBV	53	58.5	44 (14.8)	68	54.4	36.3 (11.2)	9.5
McDonald	2002	1st or 2nd degree non-familial	TBV	33	61.6	50.8 (12.9)	68	54.4	36.3 (11.2)	9.5
McDonald	2006	1st-degree	Hip	32	63.6	47.1 (13.1)	54	53.7	40.2 (15.3)	10
McDonald	2006	1st or 2nd degree familial	TBV	32	63.6	47.1 (13.1)	54	53.7	40.2 (15.3)	9
McDonald	2006	1st or 2nd degree non-familial	TBV	25	60	51.9 (13.6)	54	53.7	40.2 (15.3)	9
McIntosh	2010	≥ 2 1st or 2nd degree	TBV	72	47.2	21.2 (2.9)	36	52.8	21.4 (3.7)	9.5
Mondelli	2008	1st degree	Pit, TBV	38	50	42.2 (2.6)	46	52.2	39.7 (2.2)	10
Noga	1996	MZ twins	TBV	13	38.5	31.8 (7.7)	9	44.4	31.6 (10.7)	8
O'Driscoll	2001	1st-degree	Amy, amy-hip	20	55	36.2 (8.9)	14	64	35.4 (8.8)	9.5
Oertel	2010	1st degree	ICV	16	43.8	41.9 (8.6)	15	53.3	39.3 (11)	9.5

Oertel-Knochel	2012	1st-degree	Cau, str, hal	29	51.7	40.4 (15.9)	37	54.1	39.4 (10.5)	8.5
Owens	2012	twins	TBV	280	57	47.1 (15.7)	421	65	40.9 (13.4)	9.5
Park	2013	≥ 1 1st + ≥ 1 2nd or 3rd or 4th degree	ICV	30	56.7	26.3 (5.4)	103	38.8	25.2 (5.5)	9.5
Pirnia	2015	1st-degree	Hip, TBV	14	64.3	39.6 (11.8)	30	20	29.3 (9)	9.5
Rich	2016	offspring	Amy, cau, GM, hip, str, thal	21	43	20 (5.2)	96	55	28.8 (10.5)	9.5
Roalf	2015	relatives	Amy, cau, hip, str, thal	153	51.6	43 (18)	246	53.3	39 (16)	8.5
Schulze	2003	≥ 2 1st or 2nd degree	Hip	53	58.5	44 (14.8)	68	54.4	36.3 (11.2)	10
Schulze	2003	1st-degree	Hip	33	60.6	50.8 (12.9)	68	54.4	36.3 (11.2)	10
Seidman	1997	siblings	Amy, cau, hip, str, TBV, thal	6	100	35.8 (8)	11	100	38.4 (9.9)	8.5
Seidman	1999	1st-degree	Amy, cau, hip, str, TBV, thal	28	75	42.1 (12.7)	26	53.8	38.8 (11.5)	10
Seidman	2002	1st-degree simplex	Hip, TBV	28	64.3	41.9 (12.7)	48	43.7	40.1 (11.5)	10
Seidman	2002	1st-degree muliplex	Hip, TBV	17	58.8	38.9 (4.2)	48	43.7	40.1 (3.7)	10
Seidman	2014	siblings	Hip, TBV	27	44	27	44	19 (4.2)	48	10
Sharma	1998	parents	GM, TBV	9	54.4	59.8 (6.6)	39	48.7	33.7 (11.9)	9
Sharma	1998	1st-degree	GM, TBV	46	58.7	43.2 (14.8)	39	48.7	33.7 (11.9)	9.5
Staal	2000	siblings	Amy, cau, GM, hip, TBV	32	25	40.9 (8.6)	32	NR	NR	9
Tepest	2003	siblings	Hip	13	53.8	30.5 (5.6)	10	40	24.4 (3.5)	9.5
Van der Velde	2015	siblings	TBV	89	54	32.1 (8.1)	69	45	33.5 (10.2)	10
Van Erp	2004	MZ twins	Hip, ICV	18	50	48.5 (4.9)	56	NR	NR	9.5
Van Erp	2004	DZ twins	Hip, ICV	28	46	48.1 (5)	53	NR	NR	9.5
Van Haren	2004	Twins	Hip, TBV	10	40	36.7 (13.8)	17	29.4	38.1 (10.4)	9.5
Van Haren	2004	siblings	Hip, TBV	22	31.8	32.5 (8)	56	55.4	36 (11.7)	9.5
Wood	2005	1st or 2nd degree	Hip, TBV	35	0	19.7 (3.8)	49	0	23.6 (6.2)	9.5
Yang	2010	1st-degree (sib or par)	GM, TBV	24	45.8	31.8 (13.3)	38	52.6	26.9 (9.4)	10
Yang	2010	1st-degree (sib or par)	GM, TBV	42	66.7	55.6 (9.6)	39	56.4	56.1 (8)	10
Yan	2019	parents	TBV	60	51.7	50.7 (5.6)	28	53.6	51.8 (5.7)	10

SCZ: Schizophrenia; F: female; M: mean; MZ: monozygotic; NA: Not available; SD: standard deviation; Amy: amygdala; amy-hip: amygdala-hippocampal complex; cau: caudate; GM: gray matter; Hip: hippocampus; ICV: intracranial volume; pit: pituitary; str: striatum; TBV: total brain volume; thal: thalamus; ys: years; NR: not reported. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 6. Volumetric studies (ROI and/or whole brain volume) of BD-REL: study characteristics.

Study (First author)	Year	Kinship	Volume	Relatives			Healthy Controls			Quality score
				N	% F	age (ys)	N	% F	age (ys)	
Children										
Akbaş	2017	offspring	Amy, hip, TBV, thal	18	75	15.4 (1.6)	18	75	15.8 (1.5)	10
Bauer	2014	offspring	Amy, hip, ICV, sgCC, str	18	50	10.5 (3.4)	45	51.1	12.7 (3.3)	8.5
Handford	2015	offspring	ICV	13	38	12.5 (3)	20	45	13.3 (2.5)	9
Karchemskiy	2011	offspring	Amy, GM, HP, TBV, thal	22	68.2	12.3 (2.5)	22	68.2	13.1 (2.7)	9
Park	2015	offspring	Amy, TBV	17	37.9	13.9 (3.1)	17	52.9	14.4 (2.4)	8.5
Singh	2008	offspring (BD I)	Amy, ICV, str, thal	21	43	9.7 (1.5)	24	54	10.1 (1.5)	9
Sugranyes	2015	offspring	GM, ICV	77	45.5	12.4 (3.1)	83	53	11.8 (3.2)	9
Sugranyes	2017	offspring	GM	86	50.5	12.4 (NA)	84	61.3	12.2 (NA)	9
Van Haren	2016	offspring	GM, ICV, TBV	66	44	14.5 (2.7)	40	48	12.7 (2.1)	10
Adults										
Arnold	2014	1st-degree	hip	31	74.2	47.1 (10.7)	31	77.4	39.5 (9.9)	10
Bearden	2011	twins	GM, TBV	19	58	45.1 (8.1)	34	50	46.2 (5.4)	9
Bootsman	2015	MZ or DZ twins	Amy, hip, ICV, str, thal	37	64.6	39.3 (9.7)	129	57.3	39.1 (8.6)	10
Hajek	2008a	offspring	GM, ICV, pit	24	62.5	19.8 (3.2)	31	64.5	20.6 (3.3)	8.5
Hajek	2008	offspring (BD I)	ICV, sgCC	13	69.2	19.7 (3.3)	31	64.5	21.3 (3.5)	8.5
Hajek	2009a	offspring	GM, str	26	65.4	19.6 (3.1)	31	64.5	20.6 (3.3)	8.5
Hajek	2009 b	offspring	Amy, GM, hip	26	65.4	19.6 (3.1)	31	64.5	20.6 (3.3)	8.5
Hajek	2010	offspring	ICV, sgCC	20	55	20.2 (4.2)	18	61.1	23 (3.5)	8.5
Hajek	2013	offspring	GM, TBV	30	66.7	19.5 (3.1)	31	64.5	20.6 (3.3)	8.5
Hajek	2013	offspring	GM, TBV	20	55	20.2 (4.2)	18	61.1	23 (3.5)	8.5
Hulshoff Pol	2012	MZ or DZ twins	GM, ICV, TBV	33	66.6	41.8 (10.4)	164	56.1	37.6 (9.5)	9
Kempton	2009	1st-degree (off or sib)	ICV	50	52	33.8 (12.7)	52	48	35.2 (13)	8.5
Kieseppa	2003	same-gender twins	GM. TBV	15	60	44.5 (3.7)	27	48.1	46.7 (2.7)	8
Lancaster	2018	offspring	Amy, hip, str, thal	37	59.5	29.3 (3.8)	1005	52.1	28.8 (3.7)	9.5
Lu	2019	siblings	GM, TBV	17	52.9	42.6 (11.2)	22	40.9	42.1 (10.6)	10
Matsuo	2012	1st-degree	GM, TBV	20	75	46.2 (10.7)	40	60	41.6 (9.1)	9
McDonald	2006	1st-degree	hip, TBV	52	51.9	44 (15.4)	54	53.7	40.2 (15.3)	9
Mondelli	2008	1st-degree	Pit, TBV	38	50	42.2 (2.6)	46	52.2	39.7 (2.2)	8.5
Nery	2015	1st-degree	GM	23	60.9	31.6 (6.7)	27	59.3	31.2 (9.5)	10

Noga	2000	MZ twins	TBV, str, thal	6	83	34.5 (10.5)	22	54.5	34.7 (11)	8
Papmeyer	2016	1st or 2nd-degree	Amy, hip, str, thal	92	52.2	21.2 (2.9)	93	57	21 (2.5)	10
Roberts	2020	1st-degree	Cau, hip, str, thal	90	57.8	21 (5.5)	56	53.7	22.3 (4.2)	10
Sanches	2019	1st-degree	Amy, hip	31	74.2	47.1 (10.7)	31	77.4	39.5 (9.9)	9.5
Sandoval	2016	1st-degree	Amy	12	58.3	43.4 (19.4)	18	61.1	37.2 (12.6)	8.5
Takahashi	2010	1st-degree (off or sib)	ICV, pit	49	48.2	33.9 (12.7)	52	46.2	35.8 (13.6)	8.5
Van der Schot	2009	MZ or DZ twins	GM, ICV	50	68	40.7 (9.6)	134	57	39 (9)	9
Van Erp	2012	twins	Hip	14	38	44.6 (7.4)	32	47	47.2 (3.9)	9

BD: Bipolar Disorder; F: female; M: mean; MZ: monozygotic; NA: Not available; SD: standard deviation; Amy: amygdala; amy-hip: amygdala-hippocampal complex; cau: caudate; GM: gray matter; Hip: hippocampus; ICV: intracranial volume; ins: insula; pit: pituitary; sgCC: subgenual cingulate cortex; str: striatum; TBV: total brain volume; thal: thalamus; ys: years. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

STUDY 2: SPONTANEOUS BRAIN ACTIVITY ALTERATIONS IN FIRST-EPISODE PSYCHOSIS: A META-ANALYSIS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES

Table 1. ALFF/fALFF studies of FEP: study characteristics.

Study (First author)	Year	Antipsychotic Treatment	Patients			Healthy Controls			Quality score
			N	% F	age (ys) m (SD)	N	% F	age (ys) m (SD)	
Children									
Li	2020	Naïve	72	66.67	14.7 (1.78)	79	58.23	14.3 (2.17)	7
Liang	2019	Naïve	30	63.33	13.0 (1.4)	30	53.33	12.9 (1.4)	8
Zheng	2016	Naïve	35	42.86	15.50 (1.76)	30	56.67	15.43 (1.54)	9
Adults									
Cui	2016	Naïve	17	41.18	21.24 (3.85)	19	47.37	23.79 (3.75)	9
Cui	2016	Naïve	15	46.67	22.53 (4.07)	19	47.37	23.79 (3.75)	9
Fang	2021	Naïve	35	40.00	22.26 (5.25)	34	32.35	21.35 (2.94)	10
Fang	2021	Naïve	34	14.71	22.68 (4.66)	34	32.35	21.35 (2.94)	10
He	2013	Naïve	115	53.91	25.36 (8.26)	113	49.56	26.61 (8.90)	10
Hu	2016	Naïve	42	35.71	24.86 (4.80)	38	34.21	24.76 (4.56)	10
Huang	2010	Naïve	66	54.55	24.2 (8.4)	66	54.55	24.5 (8.6)	9
Lei	2015	Naïve	124	50.81	24.47 (6.67)	102	50.98	24.75 (6.83)	10
Li	2017	Naïve	41	43.90	23.32 (6.94)	42	42.86	23.29 (7.33)	9
Li	2017	Naïve	42	40.48	22.86 (6.70)	42	42.86	23.29 (7.33)	9
Li	2016	Naïve	20	70.00	22.9 (8.5)	16	56.25	22.4 (4.4)	9.5
Lian	2018	Naïve	18	55.56	20.44 (2.99)	30	46.67	20.53 (2.10)	8
Lui	2010	Naïve	34	61.76	24.6 (8.5)	34	61.76	25.0 (8.0)	9
Ren	2013	Naïve	100	59.00	24.30 (7.45)	100	59.00	24.39 (7.58)	9.5
Tang	2019	23/42 medicated	42	50.00	19.0 (4.0)	59	54.24	20.9 (4.0)	9
Yin	2021	Naïve	30	56.67	19.8 (3.1)	30	56.67	20.8 (2.7)	9.5
Zhao	2018	< 12 w, stop ≥ 24h	58	53.45	20.4 (3.3)	39	51.28	22.2 (4.6)	9.5

FEP: first episode psychosis; F: female; M: mean; SD: standard deviation; ys: years; NR: not reported. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

Table 2. ReHo studies of FEP: study characteristics.

Study (First author)	Year	Antipsychotic Treatment	FEP patients			Healthy Controls			Quality score
			N	% F	age (ys) m (SD)	N	% F	age (ys) m (SD)	/10
Children									
Jiang	2015	Naïve	26	50.00	14.51 (1.94)	25	52.00	14.37 (2.97)	9.5
Liu	2018	Naïve	48	56.25	15.79 (1.64)	31	54.84	15.42 (1.52)	9.5
Lyu	2021	Naïve	32	53.13	16.75 (1.22)	27	62.96	16.40 (2.12)	9
Wang	2018	Naïve	48	56.25	15.79 (1.64)	31	54.84	15.42 (1.52)	9.5
Xia	2019	Naïve	32	62.50	13.72 (2.20)	33	60.61	13.15 (2.02)	9
Adults									
Cui	2016	Naïve	17	41.18	21.24 (3.85)	19	47.37	23.79 (3.75)	9
Cui	2016	Naïve	15	46.67	22.53 (4.07)	19	47.37	23.79 (3.75)	9
Fang	2021	Naïve	35	40.00	22.26 (5.25)	34	32.35	21.35 (2.94)	10
Fang	2021	Naïve	34	14.71	22.68 (4.66)	34	32.35	21.35 (2.94)	10
Jiang	2015	Naïve	20	55.00	26.40 (8.01)	17	52.94	30.29(11.01)	9
Yan	2020	Naïve	69	27.54	24.22 (7.08)	74	39.19	26.27 (6.97)	9
Yang	2021	Stop ≥ 72h	17	17.65	31.07 (8.98)	30	20.00	34.60(10.05)	9.5
Yin	2021	Naive	30	56.67	19.8 (3.1)	30	56.67	20.8 (2.7)	9.5
Zhao	2018	< 12 w, stop ≥ 24h	58	53.45	20.4 (3.3)	39	51.28	22.2 (4.6)	9.5
Zhao	2018	Naïve	44	29.55	23.7 (5.3)	26	34.62	22.6 (3.7)	9

FEP: first episode psychosis; F: female; M: mean; SD: standard deviation; ys: years; NR: not reported. Quality score was assessed using the Imaging Methodology Quality Assessment Checklist.

STUDY 3: CORRELATIONS BETWEEN ALTERATIONS IN RESTING-STATE FUNCTIONAL CONNECTIVITY AND PSYCHOPATHOLOGICAL FEATURES IN FIRST-EPISODE PSYCHOSIS

Table 1. Demographic and clinical variables.

	FEP (n=96)	**HC (n=56)**	**χ^2 or t**	**p**
Age [m (SD), ys]	22.83±3.89	24.75±4.15	U=1896	0.002
Sex [M/F]	58/38	37/19	χ^2 =0.483	0.487
Handedness (R/L/A)	82/9/4	45/10/1	χ^2 =3.34	0.343
Full IQ	102±16.9	116±10.6	t=-5.36	<0.001
SES	2.25± 1.13	2.09 ±1.06	U=2423	0.434
AP/non AP	44/52	-	-	-
AP exposure (months)	15.56±16.16	-	-	-
AP daily dose, CPZ mg equivalents (m, SD)	165.78±217	-	-	-

A: ambidextrous; AP: antipsychotics; CPZ: chlorpromazine; F: female; FEP: first episode psychosis; HC: healthy controls; IQ: intelligence quotient; L: left; m: mean; M: male; R: right; SD: standard deviation; SES: socio-economic status

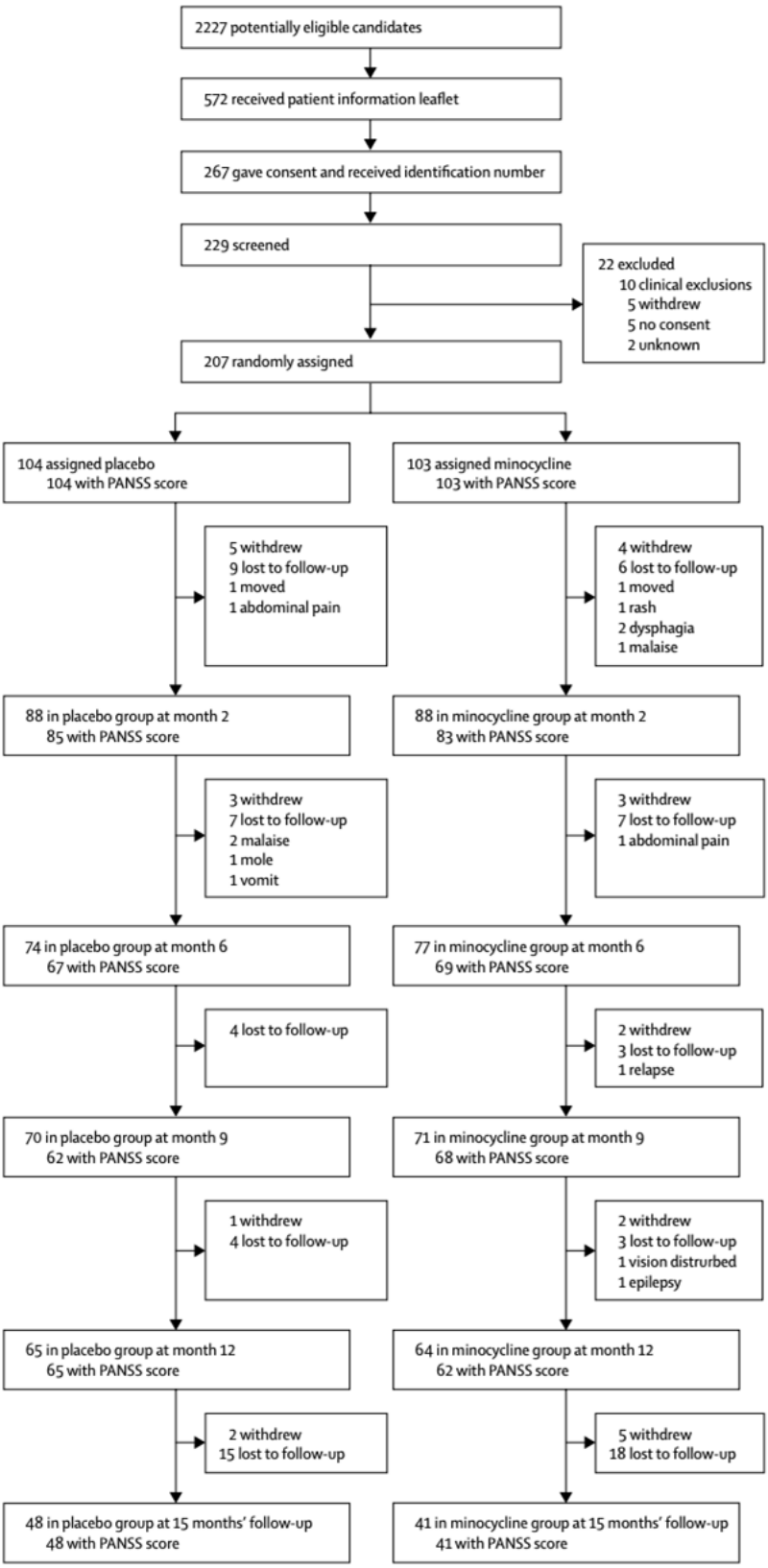
STUDY 4: PERIPHERAL INFLAMMATION AND SPONTENEOUS BRAIN ACTIVITY IN FIRST EPISODE PSYCHOSIS

Table 1. Demographic and clinical variables in the overall baseline sample and in the sample stratified by CRP levels.

	Total sample baseline (n=132)	**CRP < 3 (n=85)**	**CRP ≥3 (n=47)**	**Statistics**
Age (m ± SD, ys)	26.9 ± 5.3	25.8 ± 5.2	28.9 ± 5.0	t= -3.22 p=0.002
Sex [M/F]	95/37	23/62	14/33	χ^2=0.11 p=0.74
FSIQ	91.5 ± 14.6	92.9 ± 14.5	89.0 ± 14.7	t= 1.46 p=0.146
BMI (kg/m^2)	26.9 ± 5.3	26.0 ± 6.27	31.8 ± 7.19	U=894 p<0.001
CRP mg/l (m ± SD)	3.2 ± 4.28	0.94 ± 0.76	7.41 ± 4.87	U=0 p<0.001
IL-1RA pcg/ml (m ± SD)	457 ± 466	344 ± 392	662± 520	U=853 p<0.001
IL-1 pcg/ml (m ± SD)	0.07 ± 0.25	0.09 ± 0.29	0.17 ± 0.84	U=1910 p=0.57
IL-2 pcg/ml (m ± SD)	0.27 ± 0.25	0.28 ± 0.26	0.26 ± 0.24	U=1802 p=0.35
IL-4 pcg/ml (m ± SD)	0.02 ± 0.02	0.02 ± 0.03	0.02 ± 0.01	U=1504 p=0.01
IL-6 pcg/ml (m ± SD)	0.77 ± 0.52	0.65 ± 0.45	0.99 ± 0.56	U=1142 p<0.001
IL-8 pcg/ml (m ± SD)	4.82 ± 3.23	4.92 ± 3.6	4.65 ± 2.44	U=1858 p<0.51
IL10 pcg/ml (m ± SD)	0.40 ± 0.46	0.42 ± 0.56	0.37 ± 0.21	U=1844 p=0.47
IL-12p70 pcg/ml (m ± SD)	0.14 ± 0.18	0.13 ± 0.12	0.18 ± 0.26	U=1683 p=0.14
IL-13 pcg/ml (m ± SD)	0.55 ± 0.53	0.54 ± 0.57	0.58 ± 0.47	U=1846 p=0.47
TNF-alfa pcg/ml (m ± SD)	2.59 ± 0.66	2.51 ± 0.57	2.75 ± 0.47	U=1365 p=0.003
IFN-gamma pcg/ml (m ± SD)	5.30 ± 6.69	5.46 ± 7.80	5.01 ± 4.03	U=1686 p=0.14
PANSS positive (m ± SD)	16.3 ± 4.68	16.3 ± 4.95	16.3 ± 4.23	U=1326 p=0.73
PANSS negative (m ± SD)	16.6 ± 5.51	16.4 ± 5.91	16.9 ± 4.79	t=-0.45 p=0.65
PANSS general (m ± SD)	32.7 ± 7.42	32.0 ± 6.85	34.0 ± 8.23	U=1172 p=0.17
PANSS total (m ± SD)	65.6 ± 13.8	64.8 ± 13.4	66.9 ± 14.5	U=1218 p=0.37

BMI: body mass index; CRP: C-reactive protein; F: female; FSIQ: full-scale intelligence quotient, IFN-gamma: interferon-gamma; IL: interleukin; m: mean; M: male; SD: standard deviation; TNF-alfa: tumor necrosis factor-alfa.

Figure 1. BeneMin trial profile



STUDY 5: DYNAMIC FUNCTIONAL CONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER: A REVIEW OF THE EVIDENCE AND ASSOCIATIONS WITH PSYCHOPATHOLOGICAL FEATURES

Table 1. Selection of studies that evaluate dynamic functional connectivity in schizophrenia.

Author, year	Subjects number (M/F) Age (years) mean ± SD	Study design	MRI acquisition and dFC analysis	Clinical scales	Duration of illness (years)	Comorbidities	Medications	Neuroimaging findings	Correlations with clinical scales
Amin et al., 2018	SCZ: 144 (110/34) 38.0 ± NR	Cross-sectional	3 T SW approach k-means clustering (k = 5)	NR	NR	NR	NR	SCZ vs. HC: ↑ time in states where most ICs exhibit weaker FC. HC vs. HC: ↑ transitions in states that present high to moderate correlations among many IC.	NR
	HC: 154 (110/44) 37.0 ± NR				NA	NR	NR		
Bhinge et al., 2019	SCZ: 88 (NR) 37.0 ± 14.0	Cross-sectional	NR SW approach k-means clustering	NR	NR	NR	NR	SCZ vs. HC: reside in or switch to a state that has ↑ positive correlation within the VIS and between the anterior DMN and frontal component, VIS and parietal component, anterior DMN and frontal component, and cerebellum and VIS component. Reside in or switch to a state that has ↑ negative correlation between the cerebellum and left EXE.	NR
	HC: 91 (NR) 38.0 ± 12.0				NA	NR	NR		
Braun et al., 2016	SCZ: 28 (17/11) 33.4 ± 9.2	Cross-sectional	3 T SW approach (15 TR, 30 s) Working-memory task	SCID-I, PANSS, CGI-S	NR	NR	AP stable dose for ≥ 2 weeks	SCZ and Rel vs. HC: ↓ in network flexibility.	No significant associations between the network flexibility measure in SCZ and PANSS scores.
	Rel: 37 (8/29) 29.2 ± 11.6				NA	NR	NR		

	HC: 239 (52/87) 32.8 ± 10.1				NA	NR	NR		
Briend et al., 2020	FEP: 40 (27/23) 23.4 ± 5.8	Cross-sectional	3 T SW approach (22 TR, 44 s) k-means clustering (k = 5) ROI (EXE)	BPRS	NR	NR	AP-naïve	FEP vs. HC: ↑ FCS of the correlation of the QPP in the QPP sliding vector.	No significant associations between BPRS and the FC in the EXE.
	HC: 40 (25/15) 24.8 ± 6.4				NA	NR	NR		
Damaraju et al., 2014	SCZ: 151 (114/37) 37.8 ± NR	Cross-sectional	3 T SW approach k-means clustering (k = 5) (22 TR, 44 s)	NR	NR	NR	AP	SCZ vs. HC: ↓ time in states typified by strong, large-scale FC.	NR
	HC: 163 (117/46) 36.9 ± NR				NA	NR	NR		
Deng et al., 2019	SCZ: 40 (25/15) 26 ± 8.2	Cross-sectional	3 T SW approach k-mean clustering	SCID, PANSS	3.29 ± 3.59	NR	AP	SCZ vs. HC: ↑ mean FC variability of the whole dorsal VIS; ↑ temporal variability of the right fusiform gyrus in the dorsal network.	Significant positive correlations between the FC variability of the right fusiform gyrus and the PANSS total scores and the PANSS negative scores.
	HC: 24 (14/10) 26.5 ± 6.9				NA	NR	NR		
Deng et al., 2021	SCZ positive: 21 (13/8) 26 ± NR	Cross-sectional	3 T SW approach k-mean clustering	SCID, PANSS	2 ± NR	NR	AP	SCZ positive vs. HC and SCZ negative: ↓ mean FC-variability of the whole emotional network and the FC-variabilities in the bilateral anterior insula. SCZ positive: abnormally enhanced negative coupling between variability and FCS.	No significant correlations between any network measurement of interest and the PANSS and PANSS subscale scores in SCZ positive and negative.
	SCZ negative: 19 (12/7) 27 ± NR				2 ± NR	NR	AP		
	HC: 24 (10/14) 27 ± NR				NA	NR	NR		
Dong et a., 2019	SCZ: 96 (66/30) 39.8 ± 11.5	Cross-sectional	3 T SW approach (l = 20, 22, 24, ... 40 s) clustering Dynamic ReHo	SCID, PANSS	15.10 ± 10.3	No comorbid axis I diagnosis	AP 96	SCZ vs. HC: ↑variability of regional voxel-level FC in regions widely distributed across VIS, SM, attention, thalamus, and cerebellum SCZ vs. HC: ↑variability of FC in brain regions from VIS, SM, attention, and thalamus to the	Negative correlation between the positive PANSS subscale scores and the variability of region-to-whole-brain FC in the right lingual gyrus with

	HC: 122 (81/41) 38.0 ± 14.7				NA	No current or past axis I disorder	NA	whole brain; ↑variability of FC in brain regions from DMN and EXE to the whole brain. SCZ ↓ within-network variability in VIS, SM, and thalamus; ↓within-network variability in DMN and EXE when using two atlases (FDR corrected); ↑between-network variability in VIS-thalamus, SM-attentional, SM- thalamus, and ↓ between-network variability in DMN-EXE.	Positive correlation between the PANSS negative scores and variability of region-to-whole- brain FC in the right insula. Negative correlation between the PANSS general scores and variability of region-to-whole-brain FC in the nodes of VIS, SM, and thalamus. Negative correlation between PANSS total score and variability of FC in nodes of VIS, SM, and thalamus
Du et al., 2016	SCZ: 82 (65/17) 38.0 ± 14.0	Cross-sectional	3 T SW approach (20 TR, 40 s) k-mean clustering (k=2)	SCID, PANSS	NR	NR	NR	SCZ vs. HC: impaired interaction among DMN subsystems, reduced central role for PCC and aMPFC hubs, weaker interaction between dMPFC subsystem and medial temporal lobe subsystem.	NR
	HC: 82 (63/19) 37.7 ± 10.8				NA	NR	NR		
Du et al., 2018	SCZ: 58 (38/20) 21.8 ± 3.8	Cross-sectional	3 T SW approach (20 TR, 40 s)	SCID, PANSS, SIPS, SOPS	2.08 ± 1.37	NR	AP 53	SCZ vs. CHR: ↑ aberrant connectivities and greater alterations in the cerebellum, frontal cortex, thalamus, and temporal cortex. SCZ and CHR vs. HC: common aberrances in the supplementary motor area, parahippocampal gyrus, and postcentral cortex. CHR: specific changes in connections between the superior frontal gyrus and calcarine cortex.	NR
	CHR: 53 (32/21) 20.4 ± 4.5				NA	NR	AP-naïve 41		
	HC: 70 (41/29) 21.9 ± 5.6				NA	NR	NR		
Du et al., 2021	SCZ: 36 (NR) NR	Cross-sectional	NR time-window approach (20	NR	NR	NR	NR	SCZ vs. HC: ↓ FC and ↓ time in states in which FC between the olfactory region and hippocampus	NR
	HC: 49 (NR)				NA	NR	NR		

	NR		time points) k-mean clustering (k=5)					and frontal gyrus and vermis presented the most significant differences, ↑ FC and ↑ time in states in which FCs between postcentral gyrus and vermis and thalamus and temporal gyrus showed the most significant differences.	
Duan et al., 2020	SCZ: 42 (27/15) 24.9 ± 4.8	Longitudinal (8-week risperidone)	3 T SW approach (50 TR, 5 TR, 37 windows) ROI: insula	SCID, PANSS	< 1 year	NR	Risperidone 4–6 mg/day for 8 weeks	SCZ baseline: ↓ dFC variance between the insular subdivisions and the precuneus, supplementary motor area, and temporal cortex, ↑ increased dFC variance between the insular subdivisions and parietal cortex. SCZ after treatment: normalization of dFC variance of the abnormal connections and significant improvement in positive symptoms.	NR
	HC: 38 (25/13) 24.8 ± 4.6				NA	No	NA		
Espinoza et al., 2019	SCZ: 42 (27/15) 24.9 ± 4.8	Cross-sectional	3 T SW approach (22 TR, 44 s) k-mean clustering (k=5)	NR	NR	NR	NR	SCZ vs. HC: ↑ time in a state displaying weak connectivity between RSNs from all domains), ↓ time in states showing stronger within- and between-connectivity in the AUD, VIS, and SM domains compared to the other states.	NR
	HC: 38 (25/13) 24.8 ± 4.6				NA	NR	NR		
Faghiri et al., 2020	SCZ: 151 (NR) NR	Cross-sectional	3 T SW approach (window size 3-20) k-mean clustering (k=3) weighted average of shared trajectory (WAST)	NR	NR	NR	NR	SCZ vs. HC: ↑ time in a connectivity state with negative connectivity between motor and sensory regions.	NR
	HC: 163 (NR) NR				NA	NR	NR		

Faghiri et al., 2021	SCZ: 151 (NR) NR	Cross-sectional	3 T SW approach (10 TR, 22 s) k-mean clustering (k=8) filter-banked connectivity	NR	NR	NR	NR	SCZ: weak connection between SM and VIS/AUD networks.	NR
	HC: 163 (NR) NR				NA	NR	NR		
Fu et al., 2018	SCZ: 151 (114/37) 37.8 ± 11.4	Cross-sectional	3 T SW approach (20 TR, 40s) k-mean clustering (k=6) dALFF	NR	NR	NR	Medications	The ALFF of brain regions was highly fluctuating during the resting-state and such dynamic patterns are altered in SCZ. dALFF and dFC were correlated in time, and their correlations are altered in SCZ.	Correlation between dALFF-dFC and cognitive score.
	HC: 163 (117/46) 36.9 ± 11.0				NA	NR	NR		
Fu et al., 2020	SCZ: 151 (115/36) 38.8 ± 11.6	Cross-sectional	3 T SW approach (20 TR, 40s) Step-wise FNR	SCID, CMINDS	NR	NR	NR	SCZ vs. HC: ↑ sFNR between SC and SM/VIS/CB domains, between CB and SM/CC/DM domains, and within CB domains.	NR
	HC: 160 (115/45) 37.0 ± 10.9				NA	No psychiatric comorbidities	No psychotropic medications		
Gifford et al., 2020	SCZ: 55 (46/9) 36.1 ± 13.6	Cross-sectional	3 T SW approach (15 TR, 30 s; 25 TRs, 50 s; 30 TRs, 60 s) k-mean clustering	PANSS	15.0 ± 12.5	NR	AP	SCZ vs. HC: flexibility scores in cerebellar, subcortical and EXE, in the left thalamus and in the right crus I.	NR
	HC: 72 (49/23) 35.9 ± 11.7				NA	NR	NR		
Guo et al., 2017	SCZ: 28 (15/13) 25.4 ± 5.8	Cross-sectional	3 T SW approach (10, 11, ..., 20 volumes, equal to 20, 22, 24, ..., 40 s)	PANSS	1.3 ± 1.1	NR	AP 21	SCZ vs. HC and Rel: ↑ instability on the precuneus. Rel vs. SCZ: ↑ in medial orbitofrontal and ↓ in putamen instability.	NR
	Rel: 38 (15/13) 25.8 ± 6.4				NA	NR	No psychotropic medications		
	HC: 60 (35/25) 27.2 ± 6.6				NA	NR	No psychotropic medications		
He et al., 2019	SCZ: 42 (26/16) 42.1 ± 10.7	Cross-sectional	3 T SW approach		17.3 ± 9.9	NR	AP 42	SCZ vs. HC: ↓ dFC between CBCc and CBCm and ↓dFC	NR

	HC: 52 (29/23) 41.5 ± 12.9		(50 TR, 100 s)	SCID-I-CV, PANSS	NA	No psychiatric comorbidities	No psychotropic medications	between CBCm and cortical/subcortical networks including EXE, DMN, and SM networks.	
He et al., 2021	SCZ: 96 (68/28) 41.7 ± 11.9	Cross-sectional	3 T SW approach (50 TR, 100 s)	SCID-I-CV, PANSS	15.7 ± 10.9	NR	AP 96	SCZ vs. HC: ↓ dFC within sensory and perceptual sDFNs, ↓dFC between these sDFNs, and high-order frontal sDFNs.	Negative correlation between PANSS-positive scores and dFC within the FCS-sDFN and between the PANSS total score and connectivity between ALFF-sDFNs.
	HC: 212 (80/41) 39.9 ± 14.0				NA	No psychiatric comorbidities	No psychotropic medications		
Jia et al., 2017	SCZ: 69 (35/34) 32.0 ± 9.6	Cross-sectional	3 T SW approach (20 TRs, 40 s) SampEn ROI	DSM-IV, PANSS	7.2 ± 6.6	NR	NR	SCZ vs. HC: ↓ association between SampEn and age.	Association between SampEn between the right amygdala and the right superior orbital frontal gyrus and illness duration and between SampEn between the right amygdala and the left inferior parietal gyrus and PANSS general scores and illness duration.
	HC: 52 (25/27) 29.9 ± 8.6				NA	No psychiatric comorbidities	No psychotropic medications		
Jia et al., 2019	SCZ: 69 (35/34) 32.0 ± 9.6	Cross-sectional	3 T SW approach (20 TRs, 40 s) SampEn	DSM-IV, PANSS	7.2 ± 6.6	NR	NR	SCZ vs. HC: ↑ SampEn at the whole-brain level in the VIS and in the AUD network	Positive correlation between PANSS-negative score and SampEn of the right middle occipital gyrus. Positive correlation between PANS positive and general scores and SampEn of the right inferior occipital gyrus. Positive correlation between SampEn of the left superior occipital gyrus and illness duration.
	HC: 52 (25/27) 29.9 ± 8.6				NA	No psychiatric comorbidities	No psychotropic medications		

Li et al., 2020 (1)	SCZ: 50 (34/16) 36.5 ± 8.9	Cross-sectional	3 T SW approach (30 TRs, 60 s) ROI: LOC	NR	NR	NR	AP, AD, MD, anxiolytics	SCZ vs. HC: ↑ temporal instability of LOC connectivity over time under resting and task-switching conditions. SCZ: during rest ↑ interaction of LOC with EXE and thalamus; during task↑ interaction of LOC with the DMN.	Positive correlation between temporal instability of LOC connectivity and patients' switching cost during task performance and with hallucination severity.
	HC: 50 (29/21) 39.1 ± 6.6				NA	NR	NR		
Long et al., 2021	SCZ: 88 (NR) 37 ± 14	Cross-sectional	3 T SW approach sliding (24 TRs, 48 s) k-means clustering Graph theory	NR	NR	NR	NR	SCZ vs. HC: dysconnectivity among brain networks. ↓ centrality in frontal components	NR
	HC: 91 (NR) 38 ± 12				NA	NR	NR		
Lottman et al., 2017	SCZ: 34 (23/11) 32.4 ± 10.4	Longitudinal (6-week risperidone)	3 T SW approach (30, 40, 44, 50, 60 s) k-means clustering (k=3)	DIGS, BPRS	NR	NR	Risperidone 4.36 ± 1.45 mg at week 6. 12 benztropine, 4 AD, 1 MS	Unmedicated SCZ vs. HC: ↑ connectivity between the thalamus and somatomotor network, ↓time and fraction of time spent in the sparsely connected state, ↑time and fraction of time spent in the intermediately connected state. Risperidone normalizes mean dwell times after 6 weeks, but not the fraction of time spent.	NR
	HC: 35 (25/10) 32.0 ± 8.9				NA	No psychiatric comorbidities	No psychotropic medications		
Luo et al., 2020	SCZ: 96 (NR) NR	Cross-sectional	3 T SW approach (50 TR, 100 s)	SCID-I-CV, PANSS	NR	NR	AP	SCZ vs. HC: ↓ FCS in SAL, AUD, SM, and VIS networks, ↑ FCS in the cerebellum, basal ganglia, and EXE networks across different frequency bands.	Partial correlation between FCS of the insula, thalamus, calcarine cortex, orbitofrontal gyrus, and paracentral lobule and clinical symptoms in slow-5 and slow-4 bands.
	HC: 121 (NR) NR				NA	NR	NR		
Mannigen et al., 2019	SCZ: 58 (38/20) 21.8 ± 3.8	Cross-sectional	3 T SW approach (22 TR, 44 s)	SCID, PANSS, Kiddie-SADS	2.1 ± 1.4	NR	AP 53	SCZ vs. CHR and HC: ↑ likelihood of transitioning to a hypoconnected state. HC vs. SCZ and CHR: changes of connectivity between states that	NR
	CHR: 53 (32/21) 20.4 ± 4.5				NA	NR	AP 12		

	HC: 70 (41/29) 21.9 ± 5.6		k-means clustering (k=5)		NA	Nr	NR	were absent or altered in SCZ and CHR.	
Miller et al., 2016	SCZ: 151 (NR) 37.8 ± NR	Cross-sectional	3 T SW approach (22 TRs, 44 s) k-means clustering (k=5)	NR	NR	NR	NR	SCZ vs. HC: less dynamically active time-varying whole-brain network connectivity patterns, especially in patients with high levels of hallucinatory behavior.	NR
	HC: 163 (NR) 36.9 ± NR				NA	NR	NR		
Miller et al., 2016	SCZ: 151 (NR) 37.8 ± NR	Cross-sectional	3 T SW approach (22 TRs, 44 s) k-means clustering (k=15) ddFDC	NR	NR	NR	NR	SCZ vs. HC: ↓ FCS and dynamism.	NR
	HC: 163 (NR) 36.9 ± NR				NA	NR	NR		
Okanda Nyatega et al., 2021	SCZ: 72 (14/58) 38.17 ± 13.89	Cross-sectional	3 T SW approach (15 TRs, 30 s)	SCID	16 ± 12.4	SAFF, BD	NR	SCZ vs. HC: ↓ mean FCS between cuneus and calcarine, cuneus and lingual gyrus, cuneus, and middle temporal gyrus.	NR
	HC: 74 (23/51) 35.82 ± 11.58				NA	MDD	NR		
Rabany et al., 2019	SCZ: 33 (25/8) 24.8 ± 0.5	Cross-sectional	3 T SW approach (33 s, step = 1TR) k-means clustering (k=4)	PANSS	NR	NR	NR	Number of different states: ↓ in SCZ SCZ vs. HC: ↓ number of transitions, ↑ fraction of time in a state of weak, intra-network connectivity, ↓ fraction of time in a highly connected state, ↓ fraction of time in a widely connected state, ↑ time in the weakly-connected state, and ↓ in the highly-connected state.	No significant associations between PANSS and PANSS subscales.
	HC: 34 (23/11) 23.7 ± 0.6				NA	NR	NR		
Rahaman et al., 2021	SCZ: 151 (114/37) 37.8 ± NR	Cross-sectional	3 T SW plus clustering (22 TR, 44 s) Statelets	NR	NR	NR	NR	SCZ group statelets can characterize fewer pairs since the links are more disrupted. HC connections are more synchronized at each time point.	NR
	HC: 163 (117/46) 36.9 ± NR				NA	NR	NR		
	SCZ: 28 (23/5)		3 T		NR	NR	NR		NR

Sakoğlu et al., 2010	36.4 ± 12.4 HC: 28 (19/9) 28.8 ± 10.7	Cross-sectional	SW approach (96s)	DSM-IV TR	NA	NR	NR	SCZ vs. HC: ↑ task-modulation of motor– frontal, lateral fronto-parietal –medial temporal, and posterior DMN-parietal connections. HC vs. SCZ: ↑ task modulation of orbitofrontal–DMN and medial temporal–frontal connections.	
Salman et al., 2017	SCZ: 186 (NR) NR HC: 176 (NR) NR	Cross-sectional	3 T SW approach (22 TR, 44 s) k-means clustering (k = 3)	DSM-IV TR, SAPS, SANS, PANSS	NR NA	NR NR	NR NR	SCZ vs. HC: have ↑ state probabilities in the SM-DMN dFDC and state probabilities in VIS- DMN dFDC. ↑ entropy in the SC-SC, FRN-VIS, and DMN-VIS dFDC. ↓ CDMI in SC-SM vs. SC-VIS, SM-ATTN vs. VIS-ATTN and SM-ATTN vs. ATTN-ATTN dFDC pairs.	Positive correlation between PANSS positive scores and the VIS-FRN vs VIS-DMN CDMI.
Salman et al., 2019	SCZ: 82 (65/17) 38.0 ± 14.0 HC: 82 (63/19) 37.7 ± 10.8	Cross-sectional	3 T SW approach (26 TR and step of 1 TR) k-mean clustering (k=5) Affinity propagation clustering	NR	NR NA	NR NR	NR NR	SCZ vs. HC: ↑ dFC in SC and SM networks; ↓ FCS between AUD, VIS, and SM networks; abnormal connectivity in DMN.	NR
Salman et al., 2019	SCZ: 151 (114/37) 37.8 ± NR HC: 163 (117/46) 36.9 ± NR	Cross-sectional	3 T SW approach (22 TR, 44 s) k-means clustering (k = 3)	NR	NR NA	NR NR	NR NR	SCZ vs. HC: ↑ transformed entropy in SCZ in the following pairs: SC-SC, DMN-SC, CB-AUD, and CB-ATTN. ↓ CDMI in the following pairs: SC-VIS and SC-AUD, AUD-AUD and SC-AUD, AUD-SM and AUD-AUD, SM-ATTN and AUD-ATTN, SM-FRN and AUD- FRN, VIS-ATTN, and SM-ATTN as well as VIS-FRN and SM- FRN.	NR

Sanfratello et al., 2019	SCZ: 46 (NR) NR	Cross-sectional	3 T SW approach (22 TR, 44 s) k-mean clustering (k=4)	SCID-IV	NR	NR	NA	SCZ vs. HC: ↓ time in a state typified by strong, large-scale FC.	NR
	HC: 45 (NR) NR				NA	NR	NR		
Sendi et al., 2021	SCZ: 68 (57/11) 37.8 ± 14.4	Cross-sectional	3 T SW approach (20 TR, 40 s) k-mean clustering (k=5)	SCID-IV, SCID-I/NP interview, PANSS	< 1	NR	stable dose of AP for at least 2 months	SCZ vs. HC: ↓ dFC of ACC, ↑ dFC between the precuneus and the PCC.	Transition probability from a state with weaker precuneus/PCC and stronger ACC dFC to a state with stronger precuneus/PCC and weaker ACC dFC increased with symptom severity.
	HC: 89 (64/25) 38.1 ± 11.7				NA	No psychiatric comorbidities	No psychotropic medications		
	SCZ: 151 (115/36) 38.1 ± 11.3				< 1	NR	stable dose of AP for at least 2 months		
	HC: 160 (115/45) 37.0 ± 10.7				NA	No psychiatric comorbidities	No psychotropic medications		
Sendi et al., 2021	SCZ: 151 (115/36) 38.1 ± 11.3	Cross-sectional	3 T SW approach (20 TR, 40 s) k-mean clustering (k=5) ROI: visual sensory network	SCID-IV, SCID-I/NP interview, PANSS	< 1	NR	stable dose of AP for at least 2 months	HC vs. SCZ: ↑ dFC in cuneus and middle temporal gyrus connectivity in all states. States 2, 3: ↓ differences between HC and SCZ in the dFC of calcarine gyrus with other regions of VS.N. State 4: ↓ differences between calcarine gyrus and other regions. State 5: the greatest difference between HC and SCZ in the dFC of the middle temporal gyrus and other regions within the VS.N + significant difference in connectivity of lingual and fusiform gyri.	Positive correlation between visual learning memory and state 4 occupancy rate in SCZ.
	HC: 160 (115/45) 37.0 ± 10.7				NA	No psychiatric comorbidities	No psychotropic medications		
Sheng et al., 2021	SCZ: 51 (40/11) 38.1 ± 13.8	Cross-sectional	3 T SW approach	SCID DSM-IV	NR	NR	NR	SCZ vs. HC: ↓ FCS and ↑ variability FC widespread across the brain dynamic subnetworks.	NR

	HC: 63 (42/21) 36.3 ± 12.1				NA	NR	NR		
	SCZ: 36 (28/8) 37.2 ± 9.3				NR	NR	NR		
	HC: 60 (36/24) 33.7 ± 9.0				NA	NR	NR		
Su et al., 2016	SCZ: 25 (NR) NR	Cross-sectional	3 T SW approach (20 TRs, 40 s) k-mean clustering (k=8)	SCID DSM-IV, PANSS	NR	NR	AP 19	SCZ and Rel vs. HC: altered dFC between aPFC- right precuneus, between the leftFG- leftITG, between the left anterior insula - left ITG, between left anterior insula- the right AG, and between left ventromedial PFC - right medial occipital lobe.	NR
	Rel: 25 (NR) NR				NA	No psychiatric comorbidities	No psychotropic medications		
	HC: 25 (NR) NR				NA	No psychiatric comorbidities	No psychotropic medications		
Sun et al., 2019	SCZ: 18 (10/8) 38.8 ± 9.9	Cross-sectional	3 T SW approach (50 TRs, 100 s) temporal efficiency approach and temporal random network model	SCID-IV, PANSS, GAF	11.6 ± 8.4	NR	AP	SCZ: localized changes of temporal nodal properties in the left frontal, right medial parietal, and subcortical areas	Positive correlation between the temporal regional efficiency in the left orbitofrontal and PANSS positive scores. Negative correlation between the temporal regional efficiency in the precuneus and left temporal pole and PANSS negative scores. Positive correlation between the temporal regional efficiency in the left orbitofrontal and PANSS general scores. Negative correlation between the temporal regional efficiency in the amygdala and left
	HC: 19 (10/9) 37.7 ± 9.0				NA	No psychiatric comorbidities	No psychotropic medications		
	SCZ: 53 (41/12) 38.3 ± 13.9				15.6 ± 12.0	NR	AP		
	HC: 57 (37/20) 35.4 ± 11.9				NA	No psychiatric comorbidities	No psychotropic medications		

									temporal pole and PANSS overall scores.
Sun et al., 2021	SCZ: 28 (15/13) 16.8 ± 1.2	Cross-sectional	3 T SW approach (50 TRs, 100 s) k-mean clustering (k=6) ROI: mirror neuron system, mentalizing network	Structured Clinical Interview for DSM-IV TR, PANSS	0.7 ± 0.8	NR	AP-naïve	SCZ vs. HC: ↓ FCS between the right temporo-parietal junction and right inferior frontal gyrus and between the left inferior parietal lobe and left middle temporal gyrus; between the right temporo-parietal junction and right inferior frontal gyrus; between the right temporo-parietal junction and right inferior frontal gyrus and between right inferior frontal gyrus and left the extrastriate visual area; between the right temporo-parietal junction and right inferior frontal gyrus and between left middle temporal gyrus and left the extrastriate visual area; between the right temporo-parietal junction and right inferior frontal gyrus between left middle temporal gyrus and right extrastriate visual area.	Negative correlation between dFC between the left middle temporal gyrus and lthe eft extrastriate visual area and item 2 of PANSS negative score.
	HC: 22 (10/12) 16.3 ± 2.3				NA	NR	NR		
Supekar et al., 2018	SCZ: 35 (30/5) 34.4 ± 12.6	Cross-sectional	3 T SW approach (50 TRs, 100 s) k-mean clustering (k=2-20)	SCID, PANSS	NR	NR	AP, AD, MS, anxiolytics	SCZ vs. HC: In both cohorts, dynamic SAL-centered cross-network interactions were significantly reduced, less persistent, and more variable in SCZ.	Correlations between dynamic time-varying measures of SN-centered cross-network interactions and PANSS positive scores in both cohorts.
	HC: 35 (24/11) 36.0 ± 12.2				NA	NR	NA		
	SCZ: 30 (21/9) 31.5 ± 10.4				NR	NR	AP, AD, MS, anxiolytics		
	HC: 30 (14/16) 33.8 ± 13.1				NA	NR	NA		
Wang et al., 2016	SCZ: 30 (21/9) 31.5 ± 10.4	Cross-sectional	3 T	SCID, PANSS	14.6 ± 1.6	NR	AP	SCZ vs. HC: ↑variances of the inter-network FC between the	NR

	HC: 30 (14/16) 33.8 ± 13.1		flexible least squares (FLS) method		NA	No psychiatric comorbidities	No psychotropic medications	DMN and the EXE and between the DMN and the SAL and within the SAL.	
Wang et al., 2018	EOS: 35 (20/15) 15.5 ± 1.8	Cross-sectional	3 T SW approach (50 TRs, 100s; widow width = 30TRs/40TRs, step = 10TRs and widow width = 50TRs, step = 2TRs/5TRs) k-mean clustering (k=5)	SCID-IV-TR, PANSS	1.3 ± 1.2	No comorbid Axis I diagnosis	drug-naive	EPS vs. HC: ↓ dFC in the right middle temporal gyrus, left middle temporal gyrus, left precuneus, and left calcarine. ↑ dFC in the left cerebellum crus, left middle cingulate gyrus, right putamen, right precuneus, and right supramarginal gyrus.	Negative correlations between the left cerebellum crus1 with ↓ FC and PANSS negative scores. Negative correlations between the right supramarginal gyrus with ↓ FC and the PANSS general and total scores. Negative correlations between the right putamen with ↓ FC and the PANSS total scores.
	HC: 30 (13/17) 15.3 ± 1.6				NA	No psychiatric comorbidities	No psychotropic medications		
Wang et al., 2021	SCZ: 64 (31/33) 24.7 ± 6.8	Longitudinal (12-week AP treatment)	3 T SW approach k-mean clustering ROI: triple network	SCID-IV, PANSS, MINI	NR	NR	Baseline: drug-naive AP 64	HC vs. SCZ at baseline: mean lifetime of state 1 and state 2 ↓. After medication, the mean lifetime of corresponding brain states was significantly extended. At baseline, the mean value of dNIIs across dynamic brain states was ↓.	Significant quadratic relationship between the longitudinal change in mean dNII and the reduction ratio in PANSS total score after treatment.
	HC: 67 (32/35) 24.2 ± 6.1				NA	No psychiatric comorbidities	No psychotropic medications		
Weber al al., 2020	SCZ: 80 (59/21) 31.0 ± 11.9	Cross-sectional	3 T SW approach (20 TRs, 40 s) k-mean clustering (k=5)	ICD-1, PANSS	4.8 ± 7.7	NR	AP, AD 8, MS 6, opioids 1, anxiolytics 13, anticholinergic 4, PS 1	SCZ vs. HC: ↑ dwell time in a state characterized by mostly positive FC which was strong within networks, in particular, the DMN and LAN network, and ↓ time in a state characterized by strong positive FC within and between sensory networks and by negative FC between sensory and SC networks.	Association between hallucination proneness over 1-year and reduced dwell times in State 1.
	HC: 80 (NR) 30.9 ± 11.1				NA	NR	NR		

Yang et al., 2022	SCZ: 38 (15/23) 36.1 ± 6.2	Cross-sectional	3 T SW approach (30 TR, 22.5 s) k-mean clustering (k=5)	SCID-IV, PANSS,	11.3 ± 6.8	NR	Medications	SCZ vs. HC: ↓time in the sparsely connected state. ↓ FCS between the VIS and EXE.	Positive correlation between fraction time in state 3 and PANSS negative scores.
	HC:31 (12/19) 32.2 ± 5.8				NA	NR	NR		
Yue et al., 2018	SCZ: 33 (11/22) 30.6 ± 8.1	Cross-sectional	3 T SW approach (36 s)	SCID, PANSS	4.74 ± 2.5	NR	AP 26	SCZ vs. HC: ↑ temporal variability of FC between the left amygdala and medial prefrontal cortex.	Negative correlation between the variability of connectivity and cognitive performance on the digit symbol coding task. Marginal positive correlation between the variability of connectivity and symptom severity.
	HC: 34 (14/20) 28.1 ± 6.5				NA	NR	NR		
Zarghami et al., 2020	SCZ: 51 (43/8) 35.9 ± 13.4	Cross-sectional	3 T SW approach k-mean clustering (k=8)	SCID-I	NR	NR	NR	SCZ vs. HC: ↓ time in a globally coherent state, subcortical-centered state, and ↑ time in states reflecting anti coupling within the EXE network. Metastate occupation balance altered in SCZ. The trajectory of IPS patterns is less efficient, less smooth, and more restricted in SCZ.	NR
	HC: 68 (18/50) 35.4 ± 11.8				NA	NR	NR		
Zhang et al., 2018	SCZ AH+: 18 (9/9) 35.2 ± 13.0	Cross-sectional	3 T SW approach (100 TRs, 42.7s) k-mean clustering (k=5) ROI: eloquent language cortex in the left hemisphere	SCID-I, PANSS	5.9 ± 6.9	NR	AP 18	No significant findings were observed in any connectivity measures between ROIs at any frequency band.	No significant correlations.
	SCZ AH-: 17 (12/5) 30.0. ± 10.1				4.0 ± 3.5	NR	AP 17		
	HC: 22 (9/13) 34.9 ± 13.3				NA	NR	NR		

Zhang et al., 2021	SCZ: 34 (17/17) 27.1 ± 6.1	Longitudinal (8-week AP)	3 T SW approach (22 TR, 44 s) k-mean clustering (k=5)	SCID-I, MINI, PANSS	0.5 ± 1	NR	Baseline: drug-naïve AP 24	SCZ vs. HC: significant difference in FC variance between both groups at baseline. ↓FC variability within DMN and EXE, as well as between multiple other RSNs (i.e., DMM and AUD, SM, CC, CB; CC and AUD, CB; SM and VIS, CB). FC variability ↑ after treatment in SCZ.	Negative correlation between FC variability correlated with and PANSS total score after treatment.
	HC: 28 (13/15) 27.1 ± 4.5				NA	No psychiatric comorbidities	No psychotropic medications		

ACC: anterior cingulate cortex, AG: angular gyrus, AH: auditory hallucinations, aMPFC: anterior medial prefrontal cortex, AP: antipsychotic, aPFC: anterior prefrontal cortex, ATTN: attention, AUD: auditory, BPRS: Brief Psychiatric Rating Scale, BRSNS: between resting state network synchronization, CB: cerebellar, CBCc: Cerebellar cognitive cluster , CBCm: cerebellar motor cluster, CC: cognitive control, CDMI: Cross-Domain Mutual Information, CGI-S: Clinical Global Impression Scale , CHR: clinical high-risk, CMINDS: Computerized Multiphasic Interactive Neurocognitive System, dALFF: dynamic amplitude of low-frequency fluctuation, ddFDC: dynamic directional functional domain connectivity, dFC: dynamic functional connectivity, dFDC: dynamic functional domain connectivity, DIGS: Diagnostic Interview for Genetic Studies, DLPFC: dorsolateral prefrontal cortex , dMPFC: dorsal medial prefrontal cortex, DMN: default mode network, dNII: dynamic network interaction index, EOS: early-onset schizophrenia, EXE: executive network, FC: functional connectivity, FCS: functional connectivity strength, FEP: first-episode psychosis, FG: fusiform gyrus, FNR: functional network reconfiguration, FPN: frontoparietal network, FRN: frontal, GAF: global assessment of functioning, IPS: instantaneous phase synchrony, ITG: inferior temporal gyrus, LOC: lateral occipital cortex, MINI: Mini International Neuropsychiatric, mVN: medial visual network , MTL: medial temporal lobe, PANSS: Positive and Negative Syndrome Scale, PCC: posterior cingulate cortex , PCUN: precuneus, QPP: quasiperiodic patterns, rECN: right executive-control network , Rel: unaffected first-grade relatives, ROI: region of interest, RSNs: resting-state networks, SAPS: Scales for the Assessment of Positive Symptoms , SANS: Scales for the Assessment of Negative Symptoms, SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children, SampEn: sample entropy, SC: subcortical, SCID-IV: Structured Clinical Interview for DSM IV, sDFN: spatial organization of dynamic functional network, SIPS: Structured Interview for Prodromal Syndromes, SM: sensorimotor network, SMA: supplementary motor area, SOPS: Scale of Prodromal Symptoms, SW: sliding window, SWPC: sliding window Pearson correlation, VIS: visual.

Table 2. Selection of studies that evaluate dynamic functional connectivity in bipolar disorder.

Author, year	**Subjects number (M/F) Age (years) mean** ± SD	**Study design**	**MRI acquisition and dFC analysis**	**Clinical scales**	**Current clinical status**	**Duration of illness**	**Comorbidities**	**Medications**	**Neuroimaging findings**	**Correlations with clinical scales**
Chen et al., 2020	BD II: 128 (63/65) 26.28 ± 9.15	Cross-sectional	3T SW approach TDA ROI: striatum	HAMD, YMRS	Depression	44.2 ± 58.79 months	No comorbidities	Drug-naïve or free	BD II and MDD vs. HC: ↑ dFC variability between left putamen and left supplementary motor area and between right putamen and right inferior parietal lobule. BD II vs. MDD and HC: ↑ dFC variability between right putamen and left precentral gyrus.	No significant correlations between different dFC variability of striatum seeds and any clinical variable.
	MDD:143 (56/84) 27.68± 11.52				Depression	31.19 ± 39.86 months				
	HC: 132 (61/71) 29.09 ± 8.80				NA	NA	NR	NR		
Du et al., 2021	BD I: 35 (13/22) 31.49 ± 8.17	Cross-sectional	3T SW approach k-means clustering	DSM IV, YMRS, HAMD	Euthymia	8.51 ± 6.46 years	No comorbidities	MS 35	BD vs. HC: ↑ frequent transitions between states close to high-level cognitive networks and low-level sensory networks.	NR
	HC: 30 (15/15) 28.87 ± 7.25				NA	NA	NR	NR		
Fateh et al., 2020	BD: 40 (22/18) 34.43 ± 10.76	Cross-sectional	3T SW approach ROI: amygdala	DSM IV, HAMD	Depression	98.30 ± 92.16 months	No comorbidities	AD, MS, AP	BD vs. HC: ↓ dFC between right lateral basal amygdala and left postcentral gyrus; ↑dFC between right centromedial amygdala and right cerebellum.	NR
	MDD: 61 (28/33) 34.55 ± 10.97				Depression	58.59 ± 62.88 months		AD monotherapy		
	HC: 63 (33/30) 31.76 ± 10.58				NA	NA	NR	NR		
Han et al., 2019	BD: 40 (18/22) 34.43 ± 10.76	Cross-sectional	3T SW approach (50 TRs 100 s and 25 TRs, 50 s)	DSM-IV-TR, HAMD	Depression, euthymia, mania with psychotic symptoms	NR	No comorbidities	Medication 92.50%	BD vs. MDD vs. HC: different network switching rate of regions in DMN, SAL, and the left striatum.	NR

	MDD: 61 (33/28) 34.56 ± 11.07				Depression			Medication 98.36%	BD and MDD vs. HC: ↓ network switching rate in the key hubs of DMN.	
	HC: 63 (33/30) 31.76 ± 10.50				NA	NA	NR	NR		
Liang et al., 2020	BD I: 18 (10/8) 31.67 ± NR	Cross-sectional	1.5 T dALFF	DSM-IV, BRMS, VFT	Depression, euthymia, mania with Psychotic symptoms	NR	No comorbidities	AP, MS	BD I vs. HC: ↓ dALFF in the posterior cingulate cortex, between the posterior cingulate cortex and middle prefrontal cortex.	Positive correlation between the posterior cingulate cortex - middle prefrontal cortex dFC and the VFT in BD I.
	HC: 19 (12/7) 32.16 ±10.35				NA	NA	NR	NR		
Liu et al., 2021	BD: 20 (10/10) 35.17 ± 9.94	Cross-sectional	3 T SW approach (window length = 50 TRs, step length = 20 TRs)	HAMD, YMRS	First depressive episode	NR	No	Drug-naïve	BD depressed vs. BD euthymic: ↑ between SM and DMN and within DMN. BD euthymic vs. HC: abnormalities fronto-striato-thalamic circuit.	NR
	BD: 23 (13/10) 39.17 ± 13.10				Euthymia			Lamotrigine		
	HC: 31(16/15) 33.00 ± 8.92				NA	NA	NR	NR		
Luo et al., 2021	BD: 106 (63/65) 26.08 ± 8.66	Cross-sectional	3T SW approach dALFF Seed: bilateral precuneus + PCC	HAMD, YMRS	Depression	46.02 months ± NR	No comorbidities	Drug-naïve or free	BD and MDD vs. HC: ↓ temporal variability of the dALFF in the bilateral posterior cingulate cortex/precuneus; ↓ dFC between the bilateral posterior cingulate cortex/precuneus and the left inferior parietal lobule.	NR
	MDD: 114 (56/84) 27.81 ± 9.72				NA	29.39 ± NR		Drug-naïve or free		
	HC: 130 (61/71) 28.64 ± 8.4				NA	NA	NR	NR		
Nguyen et al., 2017	BD: 21 (7/14) 47.2 ± 11.8	Cross-sectional	3T ROI: DMN	HAMD, YMRS, PANSS, D-KEFS, Trail Making, CWI	euthymia	NR	No comorbidities	AD 48%, AP 52%, MS 67%, anxiolytics 43%	BD vs. HC: altered dFC between the middle prefrontal cortex and posterior cingulate cortex, ↓ variability in the DMN.	Association between ↓ connectivity variability and slower processing speed and
	HC: 20 (6/14) 47.3 ± 13.1				NA	NR	NR	NR		

										↓cognitive set-shifting in BD.
Pang et al., 2018	BD: 30 (14/16) 35.13 ± 9.25	Cross-sectional	3T SW approach (50 TR, 100s) ROI: the right anterior insula	HAMD	Depression	BDD: 90.23 ± 84.17 months	No comorbidities	NR	BD and MDD vs. HC: ↓ dFC between right anterior insula and right ventrolateral prefrontal cortex.	NR
	MDD: 30 (15/15) 35.27 ± 9.65				Depression	MDD: 74.67 ± 70.56 months	No comorbidities	NR		
	HC: 30 (15/15) 34.77 ± 11.17				NA	NA	NR	NR		
Pang et al., 2020	BD: 38 (19/19) 33.95 ± 9.83	Cross-sectional	3T SW approach (50 TR,100 s)	HAMD, SHAPS-14, PANAS-N	Depression	91.21 ± 76.01 months	No comorbidities	AD ± AP ± MS	BD vs. MDD and HC: ↑ FCS in the thalamus.	Combined static and dynamic FCSs predicted anhedonia severity in BDd patients and negative mood severity in MDD patients.
	MDD: 40 (20/20) 35.23 ± 10.29				Depression	MDD: 69.25 ± 68.64 Months				
	HC: 50 (24/26) 33.60 ± 10.38				NA	NA	NR	NR		
Tang et al., 2022	BD: 56 (28/28) 33.23 ± 10.79	Cross-sectional	3T DRePS	HAMD	Depression	BDD: 99.14 ± 86.09 months	No comorbidities	AD + few AP and MS	BD and MDD vs. HC: ↓ DRePS in the bilateral OFC extending to the insula, right insula extending to the hippocampus, left hippocampus, right inferior frontal gyrus and thalamus extending to caudate, right caudate, bilateral superior frontal gyrus, and right middle frontal gyrus.	No correlations in BD.
	MDD: 98 (38/60) 34.51 ± 12.15				Depression	MDD: 52.63 ± 64.98				
	HC: 97 (49/48) 33.92 ± 14.11				NA	NA	NR	NR		
Wang et al., 2019	BBD: 51 (24/27) 26.35 ± 8.79	Cross-sectional	3T SW approach (22 TRs) k-means clustering (k=3) graph theory method	HDRS, YMRS	Depression	NR	No comorbidities	Drug-naïve or free	BD VS. HC: ↑ time in a state characterized by negative correlations between the SAL, CB, BG, and sensory networks (State 2), ↓ time in a state characterized by negative correlations between the DMN and other networks	Positive correlation between time spent in State 2 and HDRS in the BD.
	HC: 50 (20/30) 28.60 ± 9.87				NA	NA	NR	NR		

									(State 3); ↑ transitions between states, ↑ dynamic variance in the small-world properties of dFC.	
Wang et al. 2020	BD: 51 (24/27) 26.35 ± 8.79	Cross-sectional	3T SW approach k-means clustering ROI: SAL, DMN, EXE	HAMD-24, YMRS	Depression	NR	No comorbidities	Drug-naïve or free	BD and MDD vs. HC: ↓ dFC variability between posterior DMN and right EXE.	NR
	MDD: 51 (22/29) 28.45 ± 8.47				Depression	NR				
	HC:52 (20/32) 29.71 ± 11.19				NA	NA	NR	NR		
Wen et al. 2019	BBD: 50 (25/25) 33.7 ± 9.89	Cross-sectional	NR SVM	HAMD-24	Depression	NR	No comorbidities	NR	BD vs. MDD: ↓ variability of dFC in SM	NR
	MDD: 50 (25/25) 35.23 ± 10.29				Depression					
	HC: 50 (24/26) 33.6 ± 10.38				NA	NA	NR	NR		
Yang et al. 2020	BD: 40 (22/18) 34.43 ± 10.76	Cross-sectional	3T SW approach (30 TRs) IHC VMHC	HAMD	Depression	NR	No comorbidities	NR	BD vs. HC: ↑ dynamic IHC in the cerebellum, inferior frontal gyrus, temporal, and SM network, ↓ dynamic IHC in the posterior parietal and precuneus.	Correlation between the number of depressive episodes and altered dynamic VMHC in the postcentral gyrus
	HC: 60 (32/28) 31 ± 10.18				NA	NA	NR	NR		
Zhang et al., 2020	BBD: 27 (16/11) 26.41 ± 8.82	Cross-sectional	3T SW approach ROI: SN	SCID-IV, HAMD-17	Depression	48 ± NR months	No comorbidities	Drug-naïve 4, free 6, medicated 18	BD vs. MDD: ↑ dFC in the left prefronto-parietal system.	No correlations in BD.
	MDD: 21 (9/12) 30.86 ±11.21				Depression	12 ± NR months		Drug-naïve 12, free 3, medicated 6		
	HC: 28 (17/11) 26.07± 4.92				NA	NA	NR	NR		

AD: Antidepressants, AP: Antipsychotics, BD: Bipolar Disorder, BRMS: Bech-Rafarlsen Mania Rating Scale, CWI: Color-Word Interference, dALFF: dynamic amplitude of low-frequency fluctuation, dFC: dynamic functional connectivity, DMN: Default Mode Network, DRePS: Dynamic Regional Phase Synchrony, D-KEFS: Delis-Kaplan Executive Function System, HAMD: Hamilton Depression Scale, HC: Healthy control, HDRS: Hamilton depression rating scale, IHC: Interhemispheric connectivity, MDD: major depressive disorder, MS: Mood Stabilizers, NA: not applicable, NR: not reported, PANSS : Positive and Negative Symptoms Scale, PANAS-N: Positive and Negative Affect Scale, ROI: region of interest, SAL: salience, SHAPS : Snaith-Hamilton pleasure, SM: Sensorimotor, SVM: Support Vector Machine, TDA: Temporal Dynamic Analysis, VFT: Verbal Fluency Test, VMHC: Dynamic Voxel mirrored homotopic connectivity, YMRS: Young Mania Rating Scale

Table 3. Selection of studies evaluating dynamic functional connectivity in bipolar disorder and schizophrenia.

Author, year	Subjects number (M/F) Age (years) mean ± SD	Study design	MRI acquisition and dFC analysis	Clinical scales	Current clinical status	Duration of illness	Comorbidities	Medications	Neuroimaging findings	Correlations with clinical scales
Das et al., 2020	Psychotic BD: 16 (11/5) 37.0 ± 9.6	Cross-sectional	3T SW approach ROI: AAL atlas	SSPI, DSST	euthymia	12.1 ± 8.0 years	NR	NR	SCZ vs. BD: asymmetric left hemispheric ↓ in FC.	Positive correlation between disorganization and ↓ left parietal d FC in SCZ.
	SCZ: 34 (25/9) 41.1 ± 9.1				clinically stable	9.6 ± 8.1 years	NR	NR		
	HC: 32 (22/10) 33.4 ± 9.1				NA	NA	NR	NR		
Du et al., 2017	Psychotic BD: 140 (53/87) 36 ± 12.57	Cross-sectional	NR SW approach ROI: AAL atlas	PANSS	euthymia	NR	No comorbidities	stable medication regimens	22 instances of hypoconnectivity (HC ↑ BD, BD ↑ SCZ) involving post-central, frontal, and cerebellar cortices. 34 instances of hyperconnectivity (HC ↓SCZ) involving thalamus and temporal cortices. Frontal connectivity: BD similar to HC	Negative correlation between hypoconnectivities in postcentral and frontal gyri and PANSS positive and negative scores.
	SCZ: 113 (56/58) 35.57 ± 12.29				clinically stable	NR	No comorbidities	stable medication regimens		
	HC: 238 (100/138) 38.15 ± 12.55				NA	NA	NR	NR		
Du et al., 2020	Psychotic BD: 140 (53/87) 36 ± 12.57	Cross-sectional	NR ROI: AAL atlas	DSM-IV-TR	Depression or euthymia or mania with psychotic symptoms	NR	NR	AP 72.14%, AD 41.43%, MS 69.29%	SCZ vs. HC: altered FC between the left postcentral gyrus and right thalamus. BD vs HC: altered FC between the left postcentral gyrus and left thalamus regions and between right	NR
	SCZ: 113 (56/58) 35.57 ± 12.29				NR	NR	NR	AP 88.50%, AD 38.94%, MS 23.01%		

	HC: 238 (100/138) 38.15 ± 12.55				NA	NA	NR	NR	thalamus and left cerebellum. SCZ vs. BD: similarity in the connectivity changes between cuneus and insula, between cuneus and putamen, and between cuneus and supramarginal gyrus. Disorder-common impairments primarily included the ↓ FCS between thalamus and cerebellum and ↑ FCS between postcentral gyrus and thalamus.	
Li et al., 2021	BD: 100 (36/64) 24.56 ± 5.95	Cross-sectional	3T SW approach K-means clustering ROI	HAMD, HAMA, YMRS, BPRS	NR	36.61 ± 36.09 months	NR	Medicated 65%	SCZ vs. BD: ↓ connectivity within VIS, SM, SAL and EXE.	NR
	SCZ: 150 (59/91) 23.67 ± 8.77				NR	23.27 ± 34.97 months	NR	Medicated 74%		
	HC: 210 (86/124) 24.37 ± 5.74				NA	NA	NR	NR		
Long et al., 2020	BD I: 53 (26/27) 25.34 ± 4.09	Cross-sectional	3T SW approach ROI: AAL atlas	SAPS, SANS, YMRS, HAMD, WAIS-I,	NR	56.99 ± 53.91 months	No comorbidities	NR	SCZ and BD vs. HC: ↑regional FC variabilities in thalamus and basal ganglia.	NR

	SCZ: 66 (38/28) 24.3 ± 6.1			WAIS-DS	NR	22.21 ± 24.97 months	No comorbidities	63 AP	SCZ vs. HC: ↑ regional FC variabilities in precentral gyrus, postcentral gyrus, inferior parietal lobule, hippocampus and amygdala, ↓ regional FC variabilities in the superior frontal gyrus. SCZ vs. BD: ↓ regional FC variabilities in the posterior cingulate gyrus. SCZ and BD vs. HC: ↑ variability for inter-network FC between the SM and thalamus. SCZ vs. HC: ↑ variabilities of both intra-network and inter- network FC in SM, VIS and subcortical networks.	
	HC: 66 (28/38) 23.38 ± 4.42				NA	NA	NR	NR		
Rashid et al., 2014	BD: 38 (18/20) 38.96 ± 10.90	Cross-sectional	3T SW approach (22 TRs, 33 s) K-means clustering (k=5)	NR	euthymia	NR	NR	NR	SCZ vs. BD vs. HC: ↑differences in SCZ from HC than BD SCZ vs. BD: differences in states of connectivity involving frontal-parietal regions	NR
	SCZ: 60 (47/13) 35.85 ± 12.01				clinically stable	NR	NR	NR		
	HC: 61 (33/28) 35.44 ± 11.57				NA	NA	NR	NR		
Zhu et al., 2020	BD: 44 (19/25) 35.0 ± 9.1	Cross-sectional	3T Functional stability	DSM-IV, SAPS, SANS,	NR	NR	NR	NR	SCZ vs. HC: ↑ functional stability in the bilateral inferior	No significant correlations between functional stability

	SCZ: 47 (12/35) 36.5 ± 8.8			HAMD, YMRS	NR	NR	NR	NR	temporal gyrus and ↓ stability in the bilateral calcarine sulcus and left insula. BD vs. HC: ↓ local stability in the left inferior temporal gyrus. SCZ and BD vs. HC: ↑ functional stability in the left inferior temporal gyrus. SCZ vs. BD: ↓ functional stability in the right calcarine sulcus.	and clinical symptoms.
	HC: 115 (53/62) 31.1 ± 8.6				NA	NA	NR	NR		

AAL: Automated Anatomical Labeling, AD: Antidepressants, AP: Antipsychotics, ATT: attentional, BP: Bipolar Disorder, BPP: Bipolar disorder with Psychosis, BPRS: Brief Mania Rating Scale, dFC: Dynamic Functional Connectivity, DMN: Default Mode Network, DSST: Digit Symbol Substitution Test, FC-rs: Functional connectivity resting state, HAMD: Hamilton Depression Scale, HAMA: Hamilton Anxiety Scale, HC: Healthy Control, MD: mood stabilizer, NA: not assessed, NR: not reported, PANSS: Positive and Negative Symptoms Scale, ROI: regions of interest, SAPS: Assessment of Positive Symptoms, SANS: Assessment of Negative Symptoms, SCZ: Schizophrenia, SSPI: Sing and Symptoms of Psychiatric Illness, WAIS-I: Wechsler Adult Intelligence Scale, WAIS-DS: Wechsler Adult Intelligence Scale Digit Symbol , YMRS: Young Mania Rating Scale

Table 4. Processing steps for the calculation of dynamic functional connectivity.

Signal extraction			
Method	*Statistics*	*Signal*	*Pros and cons*
Independent component analysis	Multivariate	Time course from mixing matrix	Pros: effective at a group scale, no prior spatial assumptions Cons: a priori number of components
Seed-based functional connectivity	Univariate (correlation)	Representative time course from ROI	Pros: effective at a subject level Cons: a priori selection of seeds
Regional Homogeneity	Univariate (KCC)	Time course similarity among neighboring voxels	Pros: no prior spatial assumptions Cons: local measure (classically 27 voxels)
Low-frequency fluctuations (ALFF, fALFF)	Univariate	Low-frequency spectrum of the voxel time course	Pros: no prior spatial assumptions Cons: limited to low-frequency band
Mirrored homotopic connectivity	Univariate (correlation)	Time course of mirror areas	Pros: interhemispheric connectivity estimation Cons: only homotopic regions are considered
dFC calculation			
Method		*Signal*	*Pros and cons*
Sliding window		Voxel-wise correlation maps	Pros: Easy to implement Cons: window size (too large does not detect small fast changes; too small does not capture variability) Low pass filtering due to the size
Filtered bank on connectivity domain		Connectivity matrices	Pros: no low-pass filter Cons: window size; high-frequency noise effects
Dynamic directional functional domain connectivity		domain-level "dynamic states"	Pros: domain level Cons: window length and domain assignment
Weighted average of shared trajectory		Trajectory of time courses	Pros: short window length Cons: nonlinear mixing
Estimation of connectivity states			
Method		*Description*	*Pros and cons*
k-means clustering		Algorithm to partition data based on the nearest means (centroid)	Pros: easy to implement, scales to large data sets Cons: local minima; influenced by noise
Principal component analysis (PCA)		Decomposition in linear orthogonal combinations of FC patterns	Pros: **removes correlated features and overfitting** Cons: ind**ependent variables become less interpretable, information loss**
Spatial and temporal independent component analysis (s-ICA)		Decomposition in linear spatially or temporally combinations of FC patterns	Pros: effective at a group scale, no prior spatial assumptions Cons: a priori number of components
Affinity propagation		Pairwise similarity that is propagated	Pros: no a priori selection of the number of clusters Cons: difficult to scale to large datasets
Statelets		similarity metric for motifs comparison (earth mover distance)	Pros: estimation of brief, repetitive co-fluctuations Cons: high time complexity and parameter tuning

ALFF: Amplitude of low frequency fluctuations, dFC: Dynamic functional connectivity, fALFF:,Fractional amplitude of low frequency fluctuations; FC: Functional connectivity, KCC: Kendall's coefficient of concordance, ROI: region of interest.

Table 5. Associations between clinical scales and dFC measures in schizophrenia and bipolar disorder.

Clinical scales		Associations between clinical scales and dFC measures
PANSS positive	SCZ	- negative correlation with the variability of region-to-whole-brain FC in the right lingual gyrus (Dong et al., 2019) - negative correlation with dFC of insula within SAL (He et al., 2021) - positive correlation with sample entropy of the right inferior occipital gyrus (Jia and Gu, 2019) - positive correlation with FCS of the left thalamus (Luo et al., 2020) - positive correlation with VIS-FRN vs. VIS-DMN CDMI (Salman et al., 2019) - positive correlation with temporal regional efficiency in the left inferior orbitofrontal gyrus (Sun et al., 2019) - positive correlation with SAL-centered time-varying cross-network interactions (Supekar et al., 2019)
	BD and SCZ	- negative correlation with the hypoconnectivities linking the postcentral and frontal gyri (Du et al., 2017)
PANSS negative	SCZ	- positive correlations with the FC variability of the right fusiform gyrus (Deng et al., 2019) - positive correlation with the variability of region-to-whole- brain FC in the right insula (Dong et al., 2019) - positive correlation with sample entropy of the right middle occipital gyrus (Jia and Gu, 2019) - negative correlation with the FCS of the bilateral insula and positive correlation with the FCS of the left orbital inferior frontal gyrus (Luo et al., 2020) - positive correlation with the probability of transitioning from a state with predominant anterior-to-posterior DMN FC relative to a state with a reverse pattern (Sendi et al., 2021b) - negative correlation with temporal regional efficiency in the right precuneus and left temporal pole (Sun et al., 2019) - negative correlation with the dFC between the left middle temporal gyrus and the visual area (Sun et al., 2021) - negative correlation with FCS in the left cerebellum crus 1 (X. Wang et al., 2019) - positive correlation with dwell time in a state characterized by sparse and weak connectivity (Yang et al., 2022)
	BD and SCZ	- negative correlation with the hypoconnectivities linking the postcentral and frontal gyri (Du et al., 2017)
PANSS general	SCZ	- negative correlation with the variability of region-to-whole-brain FC in the right lingual gyrus, bilateral precentral gyrus, and thalamus (Dong et al., 2019) - positive correlation with the sample entropy of the right amygdala and left inferior parietal gyrus (Jia et al., 2017) - positive correlation with sample entropy of the right inferior occipital gyrus (Jia and Gu, 2019) - positive correlation with the temporal regional efficiency in the left orbitofrontal gyrus (Sun et al., 2019) - negative correlation with FCS in the right supramarginal gyrus (X. Wang et al., 2019)
PANSS total	SCZ	- positive correlation with the FC variability of the right fusiform gyrus (Deng et al., 2019) - negative correlation with FCS of the left insula, positive correlation with FCS of the left thalamus, negative correlation with FCS of the left paracentral lobule (Luo et al., 2020) - negative correlation with FCS of the striato-parietal networks (X. Wang et al., 2019) - negative correlation with the connectivity between dALFF in SAL and EXE (He et al., 2021) - negative correlation with temporal regional efficiency in the right amygdala and left temporal pole (Sun et al., 2019)

		- positive correlations with FC variability of amygdala – prefrontal cortex (Yue et al., 2018) - positive correlation with the probability of transitioning from a state with predominant anterior-to-posterior DMN FC relative to a state with a reverse pattern (Sendi et al., 2021b) - negative correlation with the FC variability of VIS, SM, and thalamus (Dong et al., 2019)
BPRS	SCZ	- positive correlation between hallucination severity and temporal instability of lateral occipital cortex dFC (Li et al., 2020)
HAM-D	BD	positive correlation between: - depression severity and the dFC between the right anterior insula and the inferior parietal lobule (Pang et al., 2018) - dwell time in a state with decreased FC between DMN, SAL, and EXE (J. Wang et al., 2019)
SHAPS	BD	- positive correlation between FCS in the frontal–striatum–thalamic circuit and anhedonia in depressed BD (Pang et al., 2020)
SSPI	SCZ	- positive correlation between parietal dFC and disorganization (Das et al., 2020)

BD: Bipolar Disorder, BPRS: Brief Psychiatric Rating Scale, dFC: Dynamic functional connectivity, CDMI, Cross-domain mutual information, DMN: Default mode network, EXE: Executive network, FC: Functional connectivity, FCS: Functional connectivity strength, FRN: Frontoparietal network, HAM-D: Hamilton Depression Scale, LOC: Lateral occipital cortex, PANSS: Positive and Negative Syndrome Scale, SAL: Salience network, SCZ: Schizophrenia, SHAPS: Snaith-Hamilton Pleasure Scale, SSPI: Sign and Symptoms of Psychiatry illness, SM: Sensorimotor network, VIS: Visual network.

Table 6. Associations between cognition and dFC measures in schizophrenia and bipolar disorder.

Group	Cognitive tests	Associations between cognition and dFC measures
SCZ	visual learning memory	- dwell time in a state with positive FC within the middle temporal gyrus and between the middle temporal gyrus with other regions predicted visual learning memory performances (Sendi et al., 2021a)
	digit symbol coding task	- variability of FC in cortico-limbic circuits was associated with poorer performance on the digit symbol coding task (Yue et al., 2018)
	switching costs	- temporal instability of lateral occipital cortex connectivity predicted higher switching costs during task performance (Li et al., 2020)
BD	processing speed and set-shifting	- reduced FC variability within the DMN was associated with slower processing speed and impaired set-shifting (Nguyen et al., 2017)

BD: Bipolar Disorder, DMN: Default mode network, FC: Functional connectivity, SCZ: Schizophrenia.

STUDY 6: STATIC AND DYNAMIC FUNCTIONAL NETWORK CONNECTIVITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Table 1. Demographic and clinical variables.

	SCZ n=40	**BD n=43**	**HC n=59**	**statistics**	**p**
Age m (SD)	37.5 (8.6)	35.1 (8.9)	33.1 (8.8)	F=1.29	0.28
Sex M/F	31/9	26/17	32/27	χ^2=5.64	0.06
HAM-D m (SD)	9.4 (7.9)	12.3 (8.8)	NA	U=704	0.149
YMRS m (SD)	8.3 (7.1)	11.9 (10.7)	NA	U=702	0.156
SANS m (SD)	7.1 (4.3)	2.3 (2.3)	NA	t=-6.26	<0.01
SAPS m (SD)	9.2 (4.8)	5.1 (3.5)	NA	t=-4.44	<0.01

BD: bipolar disorder; HAM-D: Hamilton Depression Scale; HC: healthy controls; m: mean; NA: not applicable: SANS: Scale for the Assessment of Negative Symptoms; SAPS: the Scale for the Assessment of Positive Symptoms; SCZ: schizophrenia; SD: standard deviation; YMRS: Young Mania Rating Scale.