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Longitudinal changes in resting-state network connectivity in youth at familial high-risk for schizophrenia and bipolar disorder.

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Acknowledgments

Amidst the complexity of exploring mental illnesses through novel methodologies, lies the inherent beauty of this science...

In the intricate study of mental disorders using new methodological approaches, there lies the beauty of this scientific field. I want to express my heartfelt gratitude for the incredible support I have received during my thesis. I have been fortunate to have the guidance of professionals who not only taught me, but also inspired and motivated me with their enthusiasm for research in this area of healthcare.

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Furthermore, I am grateful to my family and friends who have been by my side throughout this journey, providing unwavering support and encouragement.

Summary/Abstract

Psychotic disorders present significant challenges in understanding their causes and developing effective interventions. Functional magnetic resonance imaging (fMRI) has become a valuable tool for investigating these disorders and identifying potential biomarkers. This thesis aimed to explore functional connectivity patterns in resting-state networks (RSNs) among children and adolescent offspring of individuals with Schizophrenia (SzO), bipolar disorder (BpO), and controls.

Resting-state fMRI data acquired at baseline and during a follow-up period were analyzed using statistical techniques to examine connectivity between and within RSNs associated with psychosis. The results revealed significant differences in RSN connectivity, particularly in the DMN and CEN. Abnormal functional interactions between the DMN and CEN were observed in the SzO group, indicating an aberrant dynamic between these networks. Age-related variations in connectivity patterns were also found, highlighting distinct associations between RSNs and brain maturation processes in the different groups.

The study underscores the potential of fMRI as a tool for identifying objective biomarkers. Moreover, it highlights the significance of including variables that facilitate better extrapolation to the clinical reality of psychiatry. By addressing these considerations, future research can build upon these findings and further advance our understanding of psychotic disorders.

Keywords

Resting-state fMRI, familial high-risk for psychosis, resting-state networks, schizophrenia, bipolar disorder, functional connectivity, neurodevelopment.

Preface or prologue

Psychiatry currently lacks biological markers for diagnosing, predicting treatment response, and assessing risk in mental disorders. Among these disorders, psychotic disorders are highly prevalent chronic illnesses that significantly impact patients' quality of life. However, the effectiveness of current treatments is limited, often accompanied by substantial side effects. To address these challenges, exploring the early and at-risk stages of psychosis holds promise in elucidating the underlying pathophysiology and identifying biomarkers associated with risk and resilience. By studying these critical stages, valuable insights can be gained that may lead to the discovery of novel biomarkers and ultimately improve diagnostic accuracy, treatment outcomes, and personalized care in psychiatric practice.

This study investigates functional abnormalities in individuals at familial high risk for psychosis, as psychosis disorders have a high heritability. Specifically, it focuses on offspring of patients with schizophrenia and bipolar disorders to examine the presence of functional abnormalities in this population. For the first time, the present thesis sets out to explore differences in network dynamics in familial high-risk for psychosis individuals. The observed abnormal patterns warrant further investigation, as they set a precedent for exploring functional abnormalities preceding the onset of the disease or its subclinical symptoms. These abnormalities may indicate a vulnerability to develop psychiatric disorders and have the potential to serve as risk biomarkers in clinical settings. Future utilization of these biomarkers could facilitate early intervention strategies by indicating the need for timely clinical intervention. Overall, this study sheds light on the importance of studying functional abnormalities in familial high-risk individuals and their potential implications for early detection and intervention in psychiatric disorders.

The population included in this thesis holds significant value due to the challenges associated with recruitment of familial high-risk individuals. Additionally, the study benefits from the inclusion of up to 10-year follow-up observations, which provide valuable longitudinal data. Notably, all subjects in the study underwent comprehensive clinical and neuropsychological characterization, offering an opportunity for future investigations to establish correlations between the neuroimaging findings and clinical as well as cognitive measures. This comprehensive approach ensures a robust foundation for further exploration and highlights the potential for integrating neuroimaging findings with clinical and cognitive assessments in future studies.

The absence of internet access posed obstacles, hampering the team's ability to access crucial hospital repositories and complicating the analyses. However, this adversity prompted the discovery of innovative solutions and fostered a strong sense of teamwork. The situation also reduced dependence on internet and remote connections, encouraging resourcefulness and adaptability. Despite the setbacks, this experience highlights the resilience of scientific inquiry and the ability to overcome unexpected disruptions to produce meaningful research outcomes.

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1 Introduction

1.1 Schizophrenia and bipolar disorders

Psychotic disorders, such as schizophrenia (Sz) and bipolar disorders (Bp) are currently classified into distinct conditions [1]. However, recent research has focused on the overlapping clinical, cognitive, genetic, and brain structural and functional features of these disorders [2, 3, 4, 5]. A prominent line of evidence has suggested that psychosis can be considered as a continuum with diverse manifestations, challenging the traditional notion of Sz and Bp as separate entities [6, 4].

According to the National Institute of Mental Health, Sz is a severe and chronic mental disorder. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by the American Psychiatric Association [1] categorizes Sz within the broader spectrum of schizoaffective and other psychotic disorders, together with schizotypal personality disorder, delusional disorder, schizoaffective disorder, and catatonia, among others. A complex array of symptoms characterize Sz, including positive, negative and cognitive symptoms. Hallucinations, delusions and disordered thinking are core positive symptoms, while negative symptoms characterize this illness by the absence or reduction of emotions, behaviors, and abilities, such as social withdrawal and poverty of speech [7, 8]. Cognitive impairment, including executive functioning, attention, learning, problem-solving, and social cognition, among others, also characterize this condition [9]. Along the clinical course of the disorder, positive and negative symptoms overlap and vary in severity [10].

Bp is also a chronic condition, which is characterized by recurring episodes of elevated or irritable mood (manic or hypomanic episodes) and periods of depressed mood, as well as impairment in cognitive ability [11]. Elevated and low levels of mood, energy, and activity characterize respectively mania and depression states [12]. Manic episodes disrupt normal functioning and can last from days to months, varying in severity [13]. Fluctuations between these episodes result in significant impairment in social functioning, although periods of normal mood, known as euthymia, can also be experienced [14]. Several subtypes of Bp, including Bipolar I, Bipolar II, and cyclothymic disorder, are defined and distinguished by the presence and severity of these mood episodes. Psychotic symptoms are also present in many cases, which often makes differential diagnosis challenging [15].

The estimated lifetime prevalence in the general population is approximately 3% for Sz spectrum diseases (about 1% for Sz), and 2.4% for Bp [16]. Both are identified among the most disabling and costly diseases regarding personal, social and economic costs [17]. Early onset of the disorders (before age 18) [18, 19] is associated with a poorer prognosis compared to the adult onset, with more pronounced negative symptoms, and impaired social functioning [20].

All in all, evidence suggests that Bp and Sz show both overlap and specificities in terms of clinical manifestations and underlying pathophysiology, and understanding these differences and commonalities has potential to inform clinical decisions (such as treatment and prognosis) and also to help understand the neurobiological bases of both conditions.

1.2 High-risk condition and adolescence

Risk to develop these psychiatric disorders can be conferred by multiple factors, including genetic and environmental influences [11]. In this fashion, high-risk populations are of significant interest to researchers as they provide an opportunity to unravel brain changes that occur prior to the onset of the disorder and develop new treatment strategies.

Samples at increased risk (high-risk, HR) for these conditions have been identified according to different approaches. One of the most commonly used are familial high-risk criteria (FHR), which refers to relatives of affected individuals. FHR studies rely on the fact that first degree relatives of individuals affected by these disorders have an increased risk, ranging from 10% to 15%, of developing the same disease over their lifetime [21]. Considering the risk conferred by other identified factors, such as obstetric complications [22], socioeconomic status, cannabis use [23], history of childhood trauma and stressful life events [24], familial risk is the single strongest [2, 25] risk factor for the development of Sz or Bp. Genome-wide association studies have helped identify genes closely related to psychosis, including those associated to neurotransmitter systems, synaptic function, and neurodevelopmental processes [26, 27, 28, 29, 17]. Therefore, studying child and adolescent offspring of individuals with Sz or Bp can enhance our understanding of the early phenotype and provide insights for the understanding of characteristics that may indicate the development of these psychiatric disorders.

1.2.1 Adolescence

Studies in young offspring of patients offer the advantage of assessing changes in brain and behavior during adolescence, which is a critical period of neurodevelopment that coincides with the pre-onset stages of the disease. Adolescence is characterized by significant transformations in several domains (cognitive, social, emotional), and rapid dynamic changes in both brain structure and function. Brain reorganization is thought to be influenced by synaptic pruning, in such a way that approximately 50% of synaptic connections in specific brain regions are eliminated [30]. This process is accompanied by accelerated myelination [31], contributing to enhanced brain connectivity, and development of higher-level cognitive functions, ultimately increasing adolescent brain efficiency. Disruption of such neuromaturation processes has been suggested to underlie the development of severe mental disorders, including psychosis [32, 33].

1.3 Neuroimaging

Neuroimaging approaches have the potential to enhance our understanding of the causes, prevention, diagnosis, and treatment of psychotic disorders, leading to more effective interventions and improved patient outcomes [matcheri]. Functional MRI (fMRI) provides insights into neural activation patterns and functional connectivity within the brain based on physiological and physics principles.

fMRI relies on the fact that neuronal activity involves the transmission of electri-

cal signals between cells, leading to increased metabolic demand. This generates what is known as the hemodynamic response (ie,changes in blood flow, oxygen, and glucose consumption). These physiological changes are used in fMRI to represent brain activity based on the magnetic properties of hemoglobin, which binds oxygen and exhibits variations in oxygen-rich and oxygen-poor blood, along with changes in blood flow triggered by neural activity. Hence, what is known as the blood oxygen level dependent (BOLD) signal allows the measurement of brain activity over the hemodynamic response [34]. This provides a non-invasive method to indirectly investigate neuronal activity.

This imaging technique allows to estimate and study functional connectivity (FC), which refers to the measurement of the temporal correlation of the BOLD signal between brain regions [35, 36]. It is widely accepted that this temporal correlation indicates that these regions are more likely to activate together and simultaneously (synchronous activation), and on the contrary, less likely when asynchronous activation is presented.

1.3.1 Resting state networks and adolescence

While fMRI is commonly used to observe brain activity during task performance [37], it is also applied to reveal patterns that arise when no mental activity is being performed. In 1995, Biswal and colleagues [35] discovered that the brain exhibits spontaneous, low-frequency fluctuations in the BOLD signal even when the brain is at rest. This temporal correlation of fluctuations led to the development of resting state fMRI (rs-fMRI), which enables the study of brain activity without external stimuli. The simplicity of rs-fMRI makes it particularly advantageous for investigating challenging populations, such as children and patients with psychotic disorders [38].

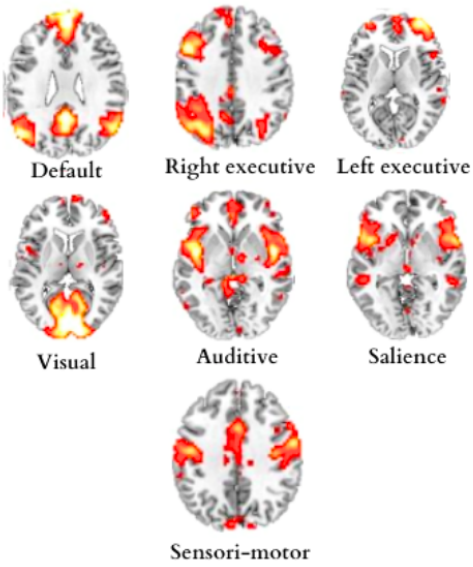


Figure 1: Main resting-state networks detected during resting-state fMRI.

During rest, spatially distributed regions of the brain exhibit what are known as resting-state networks (RSNs) [39]. These networks consist of interconnected brain regions that exhibit synchronized activity and are associated with different cognitive functions. This association has been made since, interestingly, regions that are jointly engaged during task performance, also tend to show synchronous activity during rest [40, 39].

Among the various RSNs that have been consistently identified across samples, the default mode network (DMN) is one of the most extensively investigated. It usually involves the medial prefrontal cortex (mPFC), bilateral temporo-parietal junctions (TPJ), precuneus and posterior cingulate [41]. It has been associated with self-referential thinking, introspection, and mind-wandering. Unlike other cognitive networks, the DMN exhibits deactivation during goal-directed tasks and activation during the resting-state, when the individual is not engaged in cognitive activities. Additionally, this network demonstrates a negative temporal correlation with another important RSN, the central executive network (CEN), which usually consists of the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), posterior parietal cortex (PPC), and lateral frontal cortex [42]. This network is associated with attentional control, working memory, and decision-making, and exhibits an inverse activity pattern with the DMN [43]. This switching dynamic allows for flexible cognitive functioning, thought to play a crucial role in cognitive control and attentional processes.

Another important RSN that is thought to play a role in mediating the transition between the CEN and the DMN is the salience network (SN), which usually includes the dorsal anterior cingulate and anterior insular cortices, and is thought to facilitate the shift between external attention (associated with task-focused activities) and internal attention (linked to mind-wandering and DMN activity) [44].

In 2011 Menon and colleagues proposed the 'Triple network (TN) model of major psychopathology' [45]. This approach focuses on examining both within and between-network connectivity of the DMN, SN, and CEN to help understand RSN disruption contributing to different psychiatric disorders. This framework describes the interactions between these RSNs, taking into account the primary functions of each functional network. The SN is responsible for allocating attention to salient stimuli in the environment, and either activating the CEN (cognitive control and executive tasks), or the DMN (self-referential thinking, mind wandering).

1.3.2 Brain function and adolescence

During adolescence brain connectivity tends to become more specialized. Along this process, each network enhances its intrinsic functional connectivity, differentiates from others, and optimizes its functionality [46]. The maturation of functional connectivity and global efficiency within networks reaches its peak around the age of 22 years, being adolescence a crucial stage of intermediate connectivity from less segregation to greater network pattern formation [42, 47].

Regarding intra-connectivity, the DMN develops into a more cohesive and self interconnected network [42, 48]. Within the DMN, the connectivity of the medial

prefrontal cortex (mPFC) shows the highest correlation with age, indicating ongoing maturation. Similarly, the strengthening of intra-network connectivity in the CEN is also displayed along development, and has been associated with higher IQ in children, adolescents, and adults [49] .Inter-networks connectivity displays a parallel pattern. Weaker connectivity between the DMN and the CEN is exhibited along development, leading to increased segregation of these networks [50] .However, integration of the SN with the DMN and the CEN, has proved to be notably increased in early neurodevelopment [51], which reflects the relevant role of the SN as a mediator.

Abnormal FC trajectories can contribute to cognitive and behavioral challenges during childhood. Specifically, reduced FC within the DMN [52], and excessive connectivity between the DMN and CEN have been associated with cognitive difficulties in children [53]. The dynamic interplay between these networks has been shown to have a large influence in the human neurocognitive function, and aberrant balance has been related with risk factors for developmental cognitive difficulties and for serious mental disorders [54].

1.3.3 Connectivity and psychosis

Structural and functional abnormalities have been consistently observed in Sz and Bp patients, as well as in individuals at prodromal stages and those at familial high risk (FHR) for these disorders [55]. Variations in gray and white matter have been identified, with differences potentially existing between Sz and Bp. Specifically, frontal and parietal surface area reduction has been observed in youth with Sz but not in those with Bp [56]. These structural changes may be associated with alterations in resting state networks (RSNs), which play a crucial role in brain organization and dynamics during development.

Functional abnormalities in RSNs have been found in both Sz and Bp. In Sz, hypoconnectivity within the DMN and SN has been reported, which may contribute to difficulties in self-representation and environmental salience processing [57, 58]. However, a recent study also attributes hyper-activity of the DMN in patients and HR subjects [59]. In Bp, hypo-connectivity within the DMN and hyper-connectivity within the SN, as well as hypo- and hyper-connectivity within the CEN, have been observed.

Studies assessing RSNs in individuals in the early stages of psychosis show some convergence in locating alterations predominantly in the frontal, temporal and parietal cortices [11, 60, 61, 62]. Nevertheless, specific connectivity patterns are inconsistent in the current literature. While some studies report hyperconnectivity between or within RSNs, others state that there is hypoconnectivity [60, 59, 54] .It has been suggested that this lack of consistency between patterns of connectivity between studies stems from the highly heterogeneous experimental conditions and technical procedures [63].

Fewer studies have focused on the study of RSNs in FHR individuals. Previous reports have revealed a disrupted balance in individuals at-risk for psychosis, accompanied by anatomical overlap among the DMN, CEN, and SN during spontaneous

brain activity [54, 59, 64]. Specifically, higher DMN-SN, and CEN-SN connectivity were found in both HR and first episode individuals. Moreover, HR subjects reported synchronous activation between the CEN and DMN, showing dysfunctional transitions prior to the onset of psychosis [65]. Nevertheless, a recent meta analysis [66] failed to report differences between FHR and control individuals in FC, perhaps due to the small number of studies and the high heterogeneity of these groups.

2 Aim of the study and hypotheses

The main aim of this bachelor thesis is to explore potential differences in functional connectivity, between and within the TN model, in child and adolescent offspring of individuals with Sz and Bp, compared to healthy controls. These subjects were offered a follow-up scan, which provided the opportunity to not only compare them cross-sectionally, but in terms of longitudinal trajectories. In order to achieve so, we will subdivide this objective as follows:

A) To evaluate group and group by age differences in intra-network connectivity of the RSNs involved in the triple network between controls and offspring of patients with bipolar disorder or schizophrenia , at cross-section.

B) To evaluate group and group by age differences in inter-network functional connectivity between components involved in the triple network, between controls, and offspring of patients with bipolar disorder or schizophrenia at cross-section.

C) TTo analyze inter-network functional connectivity between these components including data from follow-up assessments so as to compare if controls, and offspring of patients with bipolar disorder or schizophrenia exhibit differences in connectivity over time.

Our preliminary hypotheses associated to such objectives are the following:

A) Maps of brain network connectivity will show significantly different distributions between controls, and offspring of patients with bipolar disorder or schizophrenia, especially in the default-mode network. FHR subjects will display aberrant intra-network connectivity in anterior regions according to age, especially in schizophrenia offspring.

B) Connectivity between the default-mode network and the central-executive network will show a positive association with age in familial high risk participants when compared with controls, showing a weaker segregation between these networks. Moreover, in familial high risk subjects the salience network will be less integrated with the default-mode network and central-executive network in comparison with controls.

C) Different developmental trajectories between controls, BpO and SzO groups will be observed. The DMN and CEN will exhibit less internetwork connectivity over time in the HC group, and abnormally increasing connectivity in FHR, with a stronger effect in the SzO group. We also hypothesize that the

SN will display stronger internetwork connectivity with the DMN and CEN over time in HC than in FHR.

It is worth noting that we have created our hypotheses of the expected changes between FHR and controls and within FHR subjects in accordance with diagnosed patients associations. Few studies have addressed the TN cross-sectional comparison between these groups and associated trajectories to the date. Thus this is intended to be a first exploratory approach to the presented questions.

3 Methods

A total of 267 offspring aged 6-20 years were recruited, and followed-up with clinical and neuropsychological assessments at every visit (baseline, 2-year follow-up, 4-year follow-up, 8-year follow-up and 10-year follow-up). Additionally, every subject underwent a brain MRI scan, to collect both T1-weighted (T1w) and rs-fMRI data. The final sample of MRI acquisitions used in this study is composed of 465 acquisitions, including 95 data points in SzO, 172 in BpO, and 198 in HC (see Section 4.

Participants were eligible to be included in the study as FHR individuals if they had a parent with a diagnosis of Sz or Bp [51]. Exclusion criteria of high-risk offspring included psychotic symptoms, intellectual disability, head injury with loss of consciousness or severe neurological conditions. Participants were fully informed, parents or legal guardians provided written informed consent and participants gave their assent. For more information about the recruitment procedure, refer to a previous publication by Sanchez-Gistau [2].

The data acquisition procedure was conducted in the Child and Adolescent psychiatry and Psychology department at Hospital Clinic of Barcelona, and was approved by its ethical review board.

3.1 MRI data acquisition

Brain scans were acquired on a 3T Siemens Magnetom Trio Tim MR scanner (Tim Trio, Siemens Medical Solution; Erlangen, Germany) with a 20–channel head coil at the Magnetic Resonance Image Core Facility of IDIBAPS in the Centre for Image Diagnosis (Hospital Clinic of Barcelona).

The acquisition parameters for the T1-weighted images were: TR = 2300 ms; TE = 3,01 ms; flip angle = 9^{o}; matrix size = 256 x 256; FOV = 240 x 240 mm; slice thickness = 1; number of slices = 240; voxel size = 0.93 x 0.93 x 1. A neuroradiologist reviewed all scans to rule out radiological abnormalities.

The 8 minutes eyes-closed rsfMRI was acquired with the parameters of 240 volumes; TR = 2000 ms; TE = 29 ms; matrix size = 480 $\times$ 480; slice thickness = 4 mm, acquisition matrix = 80 $\times$ 80 mm, 32 slices, voxel size 3 $\times$ 3 $\times$ 4 mm. Participants were instructed to keep their eyes closed and stay still throughout the scanning session.

3.2 Resting-state fMRI preprocessing

The BOLD signal is not only a result of neuronal and metabolic activity, but also vascular processes [67] and may be distorted by different non-neuronal fluctuations arising from instrumental, physiological, or subject-specific factors [noise]. Thus, preprocessing is needed in order to reduce noise, correct image distortion and bring all acquisitions to the same standard space for group comparisons.

For this study, with a view to facilitate reproducibility, a standardized state-of-the-art and widely accepted pipeline was utilized: fMRIPrep version 22.1.0 [68]. The underlying principles of fMRIPrep are defined by its robustness, simplicity, and transparency. It is designed with an adaptable pipeline that applies a combination of acclaimed neuroimaging software packages to perform minimal preprocessing.

First, T1w and BOLD series were converted from DICOM to BIDS (Brain Imaging Data structure) format. Then, the workflow of fMRIprep transforms the T1w images to the standardized RAS (right, anterior, superior) coordinate system with a common voxel size (3x3x4), ensuring uniform resolution and orientation across all images. Images are skull-stripped using ANTs [69], which accurately removes non-brain tissue and generates high-quality brain masks. Subsequently, the FSL fast [70] algorithm is applied to segment the brain tissues within the masks, classifying them into cerebrospinal fluid, gray matter, and white matter. Then, the antsRegistration tool from ANTs is employed for spatial normalization to standard spaces, such as the MNI atlas [71].

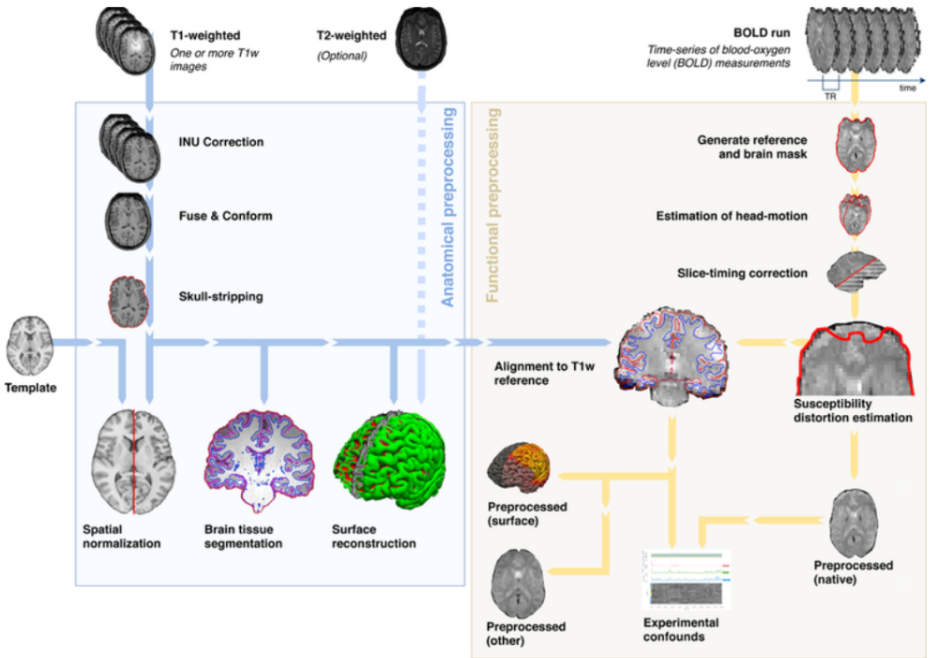


Figure 2: FMRIPrep workflow for neuroimaging preprocessing. *Retrieved from [72]*

Regarding the BOLD signal preprocessing, an estimated reference image was obtained, and a mask is generated using Niworkflows [73], which removes non-brain signals. The preprocessed BOLD volumes undergo motion and slice timing correction (adjustment of the timing of the slices, so they align with specific time points within each repetition time). The BOLD time-series are resampled onto their original, native space by Lanczos interpolation to minimize the smoothing effects of other kernels. The reference image is then used as a template for aligning the BOLD series with the T1w image of the same subject, in order to ensure spatial correspondence between both, allowing for compatibility for further comparison analyses across subjects.

Finally, as our objective is to perform Independent Component Analysis (extensively explained in section3.3), it is important to have the preprocessed BOLD resampled onto standard (MNI) space to facilitate group-level analyses across subjects for consistent spatial alignment across participants. The results of the ICA will be run on such standard space and projected back to the original space, through dual regression, as further explained in section 3.4.1.

As this research involved a large volume of data the services of Barcelona Supercomputing Center (BSC), in particular the high performance cluster StarLife, were utilized to reduce computational time by running several preprocessing pipelines simultaneously. The computational time of this preprocessing step was reduced from months to weeks.

3.2.1 Quality control and corrections

Outputs generated by fMRIPrep contain an HTML report page per subject, preprocessed data, and a CSV file containing all the aforementioned confounds.

Despite an ongoing debate regarding spatial smoothing [paper A], it remains an essential pre-processing step in current fMRI analyses, being one of the main benefits to artificially boost the signal-to-noise ratio (SNR) to enhance neural activity detection. Therefore, rs-fMRI was further smoothed by a 4 mm full-width half maximum (FWHM) Gaussian kernel[74]. Then a temporal band-pass filter was applied to remove noise and high-frequency components between 0.01-0.1 Hz [75].

Motion confounding data was then used for the Quality Control (QC) of the images. Thus, subjects with average motion exceeding a strict threshold (FD > 0.2) were excluded [72]. Then, according to ENIGMA standards [76], visual inspection was done to check registration alignment and noise artifacts. Subjects with incomplete acquisitions were discarded. Afterward, a custom Python script was employed to analyze the confounds file from fMRIprep output, identifying critical volumes that exceed the predetermined threshold for each variable and generating matrices for FD, DVARS, and movement parameters. These matrices were then utilized as regressors to correct for their respective effects.

3.3 Neuroimaging processing: ICA

An Independent Component Analysis (ICA) was applied to denoised rs-fMRI images with a successful QC. ICA is a data-driven approach that concatenates the fMRI data from all subjects and splits the BOLD signal into the spatial brain areas that display correlated fluctuations [75]. As a result, a set of independent components (ICs) representing spatio-temporal patterns of activity were obtained.

Given the methodological processing was extremely time consuming, and considering that access to the BSC was obtained after a period of attempting to preprocess the entire sample, the analysis initially began with a cross-sectional study, which is often the first step in exploratory analyses. Later, the complete dataset was obtained. For this reason, the decision was made to conduct the cross-sectional analysis as a first approach and then examine whether adding longitudinal data yielded different or more robust results. Therefore, the entire workflow was replicated for the baseline acquisition data (cross-sectional study) and the complete dataset (longitudinal analysis).

Considering the twofold structure of the study (i.e., cross-sectional analysis and analysis with the complete sample), two distinct ICAs were performed.

1. Cross-sectional ICA, which included the unique baseline acquisition per subject.
2. Whole sample ICA, which included all available acquisitions from all participants.

These analyses were carried out using the MELODIC function of FSL [70] ,and the number of extracted components was set to 20 ICs, which matches a common degree of clustering applied on multiple studies [77]. However, components that corresponded with white matter, cerebrospinal fluid or venous sinus were then excluded from further analyses.

Note that from this point onwards, following the separate ICA results, all methodology steps were repeated twice for each dataset set.

3.4 Triple network selection

In order to focus on the study of the TN, the three involved RSNs (i.e., DMN, SN, CEN) were selected from the initial set of 20 independent components (ICs). In order to do so, the templates from Yeo and colleagues [36] were used to visually and empirically test the spatial Pearson cross-correlation between the 20 ICs and the predefined RNSs.

Cross-correlations between every volume in the template with every volume in the selected ICs was performed in Python employing the 'fslcc' command from FSL package [70]. The threshold for statistical significance was set at $p < .01^{**}$ and the correlation threshold at $r > 0.2$. Higher correlation coefficients were used as indicators for a first selection of the ICs that better fit with the DMN, CEN, and SN. Then, visual inspection was conducted in 'fsleyes' FSL tool [70] to validate the correct selection of components.

A total of 6 ICs from the cross-sectional group-ICA were selected to depict the TN after spatial correlation and visual inspection.

Similarly, when testing the complete dataset, 6 ICs from the longitudinal group-ICA were selected after spatial correlation and visual inspection. Components selection and correlation coefficients are shown in Figure 3.

Our experimental results suggest that the DMN is composed of two ICs, one for the anterior part in the mPFC (aDMN), and another that fits almost with the whole network (gDMN). One unique component represents the SN. Finally, the CEN is fragmented into three subregions. A different IC is labeled to represent from now on the right, left, and bilateral functional domains (rCEN, lCEN and bCEN, respectively).

Although the subdivision of a network into different ICs made the following analyses more complex, it is a consequence of the network fragmentation into different functional domains. This allows us to study how different sections of the same network interact, showing intra-network connectivity patterns.

3.4.1 Dual Regression analysis

In order to extract the contribution of each subject to the selected ICs and investigate inter-group comparisons, a dual regression (DR) was performed. This approach involves two main steps (see Figure 4).

First, the spatial maps of the ICs obtained from the group ICA are used as a template to regress into each subject's data, aiming to identify the contribution of each spatial map to the individual subject's data. The result of this first stage is a set of time courses specific to each subject, representing the specific activation patterns associated with each group-level spatial map. This enables the quantification of the contribution of each subject to the identified ICs.

In the Stage 2, time courses are regressed back, meaning that they are projected into the original data space. This allows us to map subject-specific spatial data, which represent the individual connectivity patterns for all the ICs.

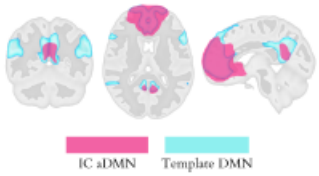
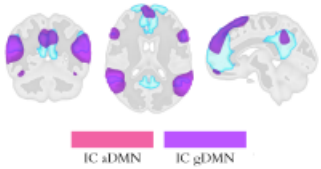
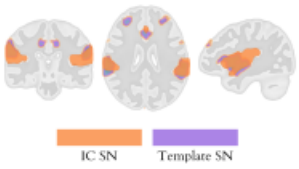
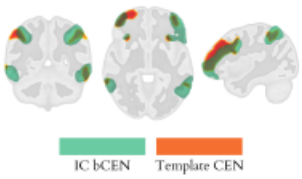
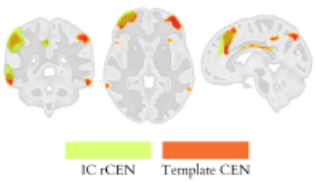
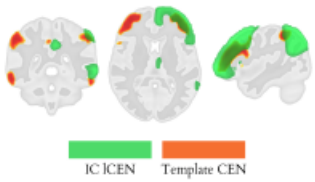
	Visual inspection	Correlation (r)
DMN components		**Anterior DMN (aDMN)** 0.4
		**General DMN (gDMN)** 0.54
SN components		**SN** 0.6
CEN components		**Bilateral CEN (bCEN)** 0.56
		**Right CEN (rCEN)** 0.5
		**Left CEN (lCEN)** 0.42

Figure 3: Longitudinal group-ICA ICs identified as regions that represent the TN. Visual representation of the selected ICs over the Yeo template [36] and correlation coefficient of spatial correspondence.

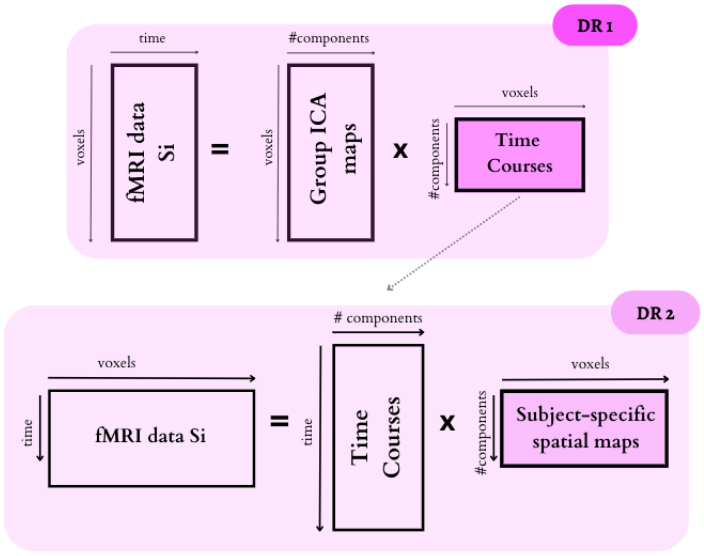


Figure 4: Dual regression analysis explained in the two stages that allow to find the time courses and spatial maps for each subject using the Group ICA maps obtained from the ICA analysis.

3.4.2 Correlation matrices

Next, using the DR output, a temporal correlation of the time-courses of the selected ICs was performed to further explore inter-network connectivity. To achieve so, the subselection of ICs were correlated using pairwise Pearson correlation, by employing a customized version of the FSLnets toolbox of FSL [70]. To ensure inter-subject comparability, the resulting connectivity matrices, containing the correlation between ICs, were converted to z-scores using Fisher's transformation.

3.5 Statistical analyses

3.5.1 Demographic variables

Demographic characteristics of FHR participants are summarized in Table 1. Initially a selection of 267 subjects were included in the sample. However, after QC we ended up with 243 subjects with 465 longitudinal assessments. For cross-sectional analysis, the sample was initially paired by age and sex, resulting in a reduced sample size (see Table 2).

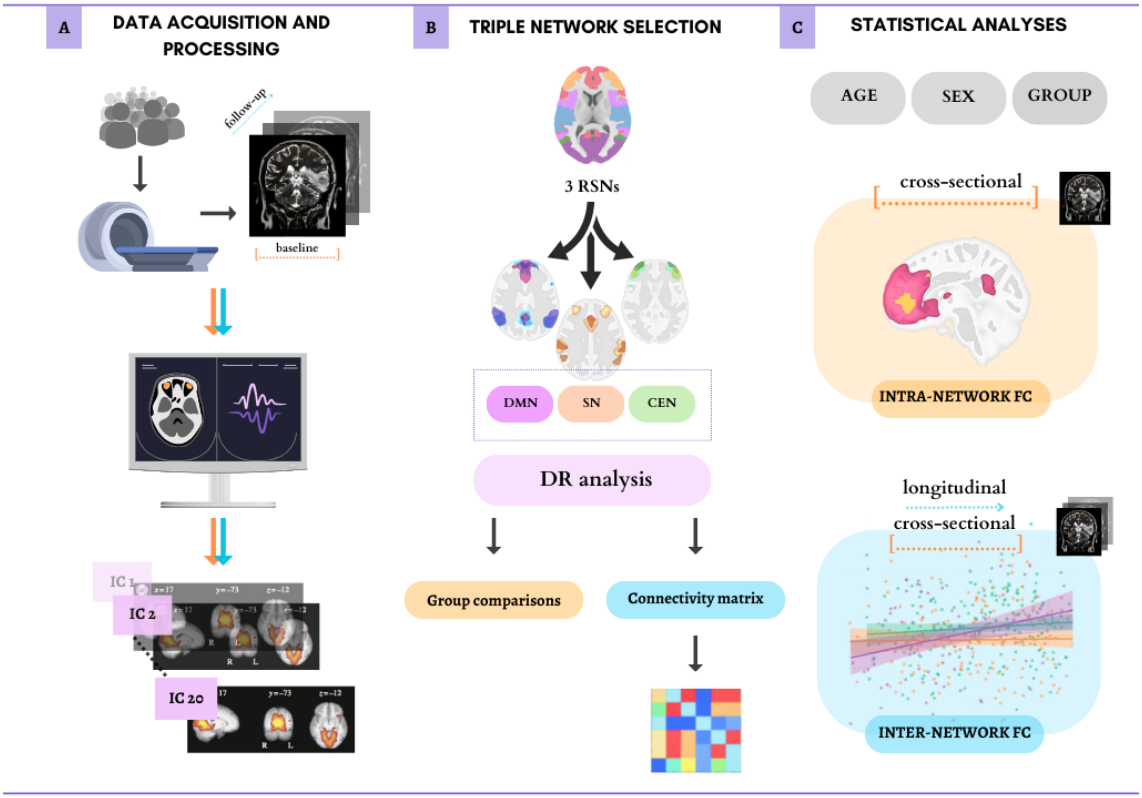


Figure 5: Methodological pipeline followed in this study. ***A. Data acquisition.*** First, MRI data was previously acquired through the Magnetic Resonance Image Core Facility of IDIBAPS in the Centre for Image Diagnosis (Hospital Clinic of Barcelona). Once the data was available, it was organized and prepared as required input for the preprocessing fMRIprep standardized workflow. Next, ICA analysis was performed to extract group maps. ***B) Triple Network selection.*** Identification of components representing the TN by using a RSNs template was performed empirically and by visual inspection. DR analysis was performed to extract specific time-courses of each subject, used then to further assess intra-network connectivity in cross-sectional data. Time-courses were also used to create FC matrices, by applying pair-component temporal correlations. ***C) Statistical analyses.*** Two different analyses were conducted. First, intra-network connectivity was explored in the TN components at cross-sectional. Moreover, analysis of variance (ANOVA) tests were employed to analyze different linear hypotheses and assess the statistical significance of group effect -and its interaction with age- in the correlation of pairs of the ICs of interest. Age association was studied for the cross-sectional sample, while age trajectories were assessed for longitudinal data.

3.5.2 Group comparisons

After identifying the TN components and extracting the contribution of each subject to these RSNs, the Randomise function of FSL [78] was utilized to perform pairwise comparisons between groups, individually for each network component.

This statistical tool is designed for non-parametric permutation testing, commonly used to assess differences between groups in neuroimaging studies, when the hypoth-

esis testing does not rely on specific distributional assumptions. It works by conducting a large number of permutations of the data. It assigns randomly the group labels to all the observations, shuffling the data while preserving spatio-temporal characteristics. Then computes a test statistic for each permutation. All the permutations are later compared with the observed test statistic, which generates a null distribution (i.e, under the assumption of no difference between groups). Based on the null distribution, Randomise calculates the p-value for each observed test statistic, indicating the probability of obtaining a test statistic as extreme or more extreme than the observed value by chance alone, assessing for statistical significance.

This method provides a robust and unbiased approach to assess group differences while effectively managing multiple comparisons. Finally, in order to capture patterns of distinction between the groups of the analysis, we employed threshold-free cluster enhancement (TFCE) for the comparisons. This technique enhances the sensitivity to detect significant clusters in neuroimaging data without the need to define an arbitrary threshold. It considers both the spatial extent and intensity of activation, providing a more comprehensive analysis of group differences[79].

To guide the analyses, a design matrix was created to include group effect and sex and age as covariates. Also, a contrast file was generated to specify the pairs of comparisons to perform. Four different contrasts include the main independent effects of the three variables:

- the interaction between group - age accounting for the influence of sex.
- the interaction between group - sex accounting for the influence of age.
- the three-way interaction effect between group-age-sex.

A minimal voxel difference threshold (10 voxels) was applied to ensure the detection of meaningful differences between groups. Finally, Bonferroni correction was applied to account for multiple comparisons.

3.5.3 FC analysis: Linear and mixed models

As for the inter-network correlation matrix comparison, linear regression analyses were employed in RStudio software [R] to explore the relationship between age, group and inter-network FC, while accounting for gender as a covariate. Linear regression is a statistical technique used to model the relationship between a dependent variable and one or more independent variables.

In our analysis, the inter-network FC accounts for the dependent variable. Group and age are the independent variables, used to predict the FC. The model finds the coefficients associated with each independent variable, considering also an intercept term (expected value of dependent variable when all independent variables are zero), and an error term that captures the unexplained variability in the model.

Next step was to employ Analysis of variance (ANOVA) tests to analyze linear hypotheses and assess the statistical significance of the group, and the interaction of the group with age in the inter-components FC of the TN. The multicomp package

from Rstudio [80] was used to perform univariate testing via z- and t-tests of estimated model coefficients. Statistical significance was studied by analyzing p-values before and after adjusting with False Discovery Rate correction (FDR)[1].

The same procedure was repeated for the longitudinal data. However, in this case, a mixed-effects model was employed to study the linear hypothesis, including the subject as a random effect. This modeling approach allows examining the same associations mentioned earlier while accounting for multiple observations from the same subject (within-subject dependence)[82].

[1]This is a statistical method used to control for multiple comparisons in hypothesis testing, ensuring a more rigorous and reliable analysis. Significance was considered for values below the threshold of $p<.05$* (note that FDR corrected p-value of .05 means that 5% of "declared" positive results are truly negative)[81]

4 Results

4.1 Sample

After QC, a total number of 243 subjects were included in the longitudinal analysis, with 465 acquisitions, including 95 data points in SzO, 172 in BpO, and 198 in HC. Among the participants, 100 individuals had a single baseline acquisition, 84 individuals were assessed at two different time points, 41 subjects had acquisitions at three different time points, 16 individuals had four, and 2 individuals had 5 evaluations, along the follow-up period.

Characteristic	N	HC, N = 198[1]	BpO, N = 172[1]	SzO, N = 95[1]	p-value[2]
AGE	465	198: 16.2 (7.2, 26.9)	172: 15.7 (6.1, 27.7)	95: 13.4 (6.1, 23.2)	<0.001
SEX	465				0.053
Male		86 (43%)	77 (45%)	55 (58%)	
Female		112 (57%)	95 (55%)	40 (42%)	

[1] N: Mean (Range); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Table 1: Demographic description of the longitudinal dataset used for this study.

4.1.1 Cross-sectional dataset

For the purpose of performing a cross-sectional analysis, a subset of the sample was made, including only the baseline acquisitions from each subject. To ensure comparability and control for potential confounding factors, the sample was paired by age. Due to the pairing and QC procedures, several subjects were excluded from the analysis, resulting in a reduced dataset described in Table 2.

Characteristic	N	HC, N = 91[1]	BpO, N = 59[1]	SzO, N = 39[1]	p-value[2]
AGE	189	91: 14.4 (7.3, 20.4)	59: 13.7 (6.1, 20.9)	39: 12.2 (6.3, 18.8)	0.006
SEX	189				0.13
Male		34 (37%)	26 (44%)	22 (56%)	
Female		57 (63%)	33 (56%)	17 (44%)	

[1] N: Mean (Range); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Table 2: Demographic description of the cross-sectional dataset used for this study, after age pairing.

4.2 Triple-network connectivity analyses

A. Cross-sectional spatial group comparisons

When analyzing group and group by age effects in the FC of the whole brain components, a cluster of 175 voxels was located in the anterior component of the DMN (See Figure 6)). Within this cluster, individuals with schizophrenia exhibited greater connectivity associated with age compared to the BpO group. Notably, no significant group by sex effects were observed.

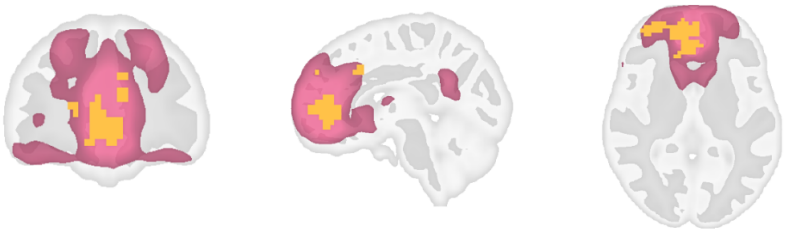


Figure 6: In pink, the DMNa component of the cross-sectional analysis. In orange, the significant voxels obtained when comparing group-age interaction between BpO and SzO groups.

B. Cross-sectional between-component connectivity

In the next analysis, we examined potential variations in the relationship between age and functional connectivity between networks across groups.

The findings revealed that mean inter-network FC between the SN and aDMN exhibited statistically significant differences between the BpO and HC groups, with higher values in the BpO group (see box-plot representation in Figure 7).

Group comparison	RSNs	Estimate	SE	t-value	p(>|t|)	FDR p
BpO vs HC	SN - aDMN	0.0612	0.0268	2.279	<.05*	0.25

Table 3: Inter-components connectivity by group effect (cross-sectional).

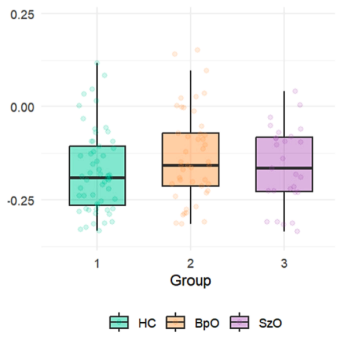


Figure 7: FC between SN and aDMN in each group (cross-sectional).

We further investigated potential variations in the association between age and FC across the different groups. Significant differences were found in two pairs of network components.

Firstly, the connectivity between the rCEN and lCEN displayed a more pronounced negative association with age in the SzO group compared to the HC group. Additionally, the correlation between the SN and aDMN exhibited a significant group difference in the BpO with respect to HC group, demonstrating a decrease with age in the first group.

Group comparison	RSNs	Estimate	SE	t-value	p(>|t|)	FDR p
SzO vs HC	rCEN-lCEN	-0.0242	0.0111	-2.178	<.05*	0.11.
BpO vs HC	SN - aDMN	-0.0190	0.007	-2.248	<.05*	0.23

Table 4: Inter-components connectivity by group*age effect (cross-sectional).

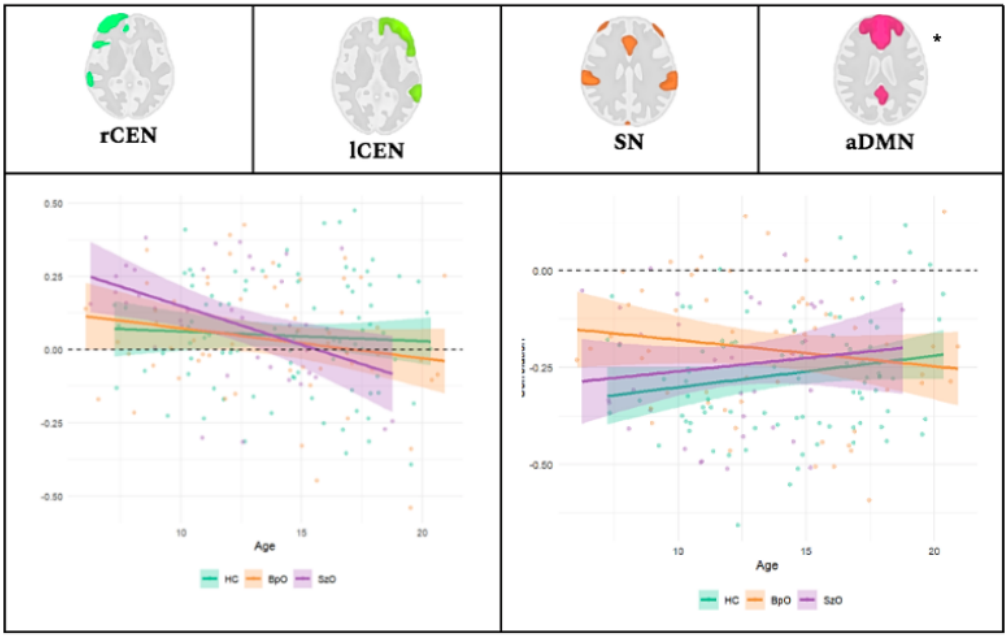


Figure 8: Connectivity by age association followed in each group when observing the correlation values between: A) rCEN with lCEN. B) SN with aDMN.

C. Inter-component connectivity: longitudinal analysis

In this analysis, we explored potential variations in the relationship between age and FC between networks across different groups using longitudinal data. The connectivity between bCEN and gDMN exhibited higher values in the SzO group when compared to the HC group. Additionally, the BpO group showed a similar effect, although to a lesser extent compared to the SzO group.

Group	RSNs	Estimate	SE	z-value	p(>|z|)	FDR p
SzO vs HC	bCEN - gDMN	0.0857	0.0263	3.634	<.001***	0.09.
BpO vs HC	bCEN - gDMN	0.0646	0.0223	2.892	<.01**	0.2

Table 5: Inter-components connectivity by group effect (longitudinal).

Next, we investigated potential variations in inter-network FC over time across the different groups, revealing two differences. First, the connectivity between the bCEN and gDMN demonstrated a positive relationship with age in the SzO group compared to the HC group. Additionally, when examining the inter-network strength between the rCEN and lCEN, the SzO group exhibited disconnectivity.

Group	RSNs	Estimate	SE	z-value	p(>|z|)	FDR p
SzO vs HC	bCEN - gDMN	0.0116	0.0057	2.023	<.05*	0.17
SzO vs HC	rCEN - lCEN	-0.0109	0.0051	-2.225	<.05*	0.12

Table 6: Inter-components connectivity by group*age effect (longitudinal).

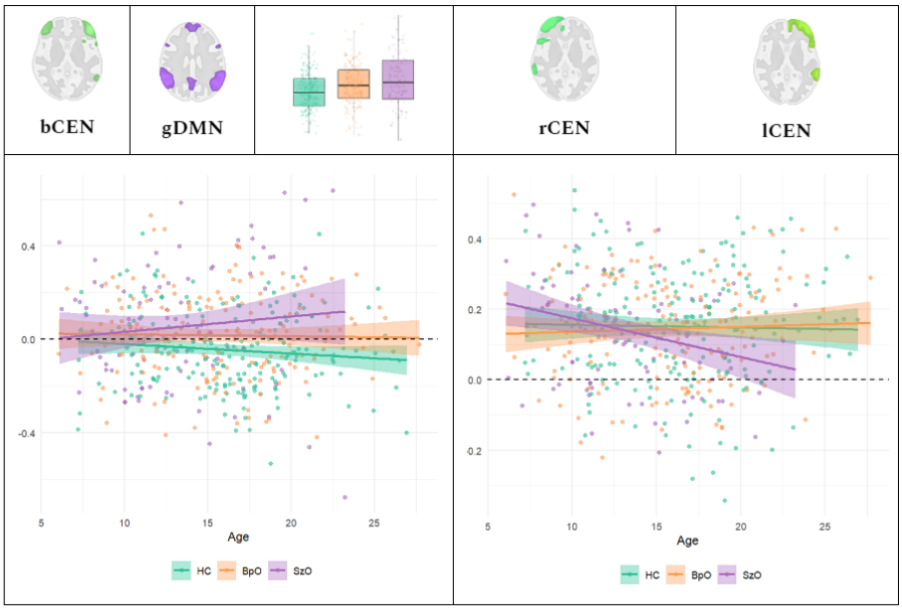


Figure 9: Connectivity by age association followed in each group when observing the correlation values between: A) rCEN with lCEN. B) SN with aDMN. Note that the boxplot representation is the one corresponding to the group effect observed in the bCEN-gDMN connectivity.

Note that none of these results survived after correction for multiple comparisons.

5 Discussion

The present bachelor thesis aimed to investigate FC in a selection of RSNs that have demonstrated abnormal activity in individuals with Bp or Sz. Since these disorders show high heritability, the main focus of this study was to determine whether the differences in FC also manifest during childhood and adolescence in high-risk offspring of patients with Sz or Bp in relation to controls.For this purpose, intra and inter-network connectivity were studied to explore how age,group and their interaction had an effect on these measures.

Cross-sectional RSNs spatial group comparisons

Group comparisons between the six ICs that represent the TN revealed significant differences between a cluster of voxels within the anterior component of the DMN. Higher connectivity was associated with age in the SzO group, indicating a distinctive FC association between this and the BpO groups. Despite discrepances, this feature has been suggested as a biomarker for Sz, also detected in older unaffected relatives [83]. Moreover, is consistent with our hypothesis ***A***, since SzO display aberrant intra-connectivity in the anterior region of the DMN, which overlaps with findings in the mPFC as a relevant region of interest for psychosis.

Cross-sectional inter-component correlation group comparisons

When the temporal correlation between ICs was studied, a group effect was observed cross-sectionally in the inter-network strength connectivity of the BpO group, with respect to controls. Salience integration with the aDMN seems to be stronger in these subjects, while it has not been associated with symptomatology in current literature. However, this higher connectivity seems to display a more drastic association with age, in terms of a negative association in the BpO group compared with HC. Abnormal trajectories in early-onset of Bp have been reported with respect to the FC of these networks [84]. This demonstrates that not only the strength of connectivity in this group, but also the association in different stages, differs from controls and can provide more revealing information. Better integration of these two RSNs has been established as a normal feature of neuromaturation, allowing a better control of the switch between the DMN and CEN.

Secondly, the correlation between rCEN and lCEN demonstrated a more pronounced negative association with age in the SzO group compared to the HC group. Here we have two subcomponents of the same network (CEN), which can be interpreted as a weaker integration of this RSN in older SzO subjects. This is consistent with our hypothesis ***B***, based on patients, which states a weaker integration within individual RSNs as an abnormal pattern.

Longitudinal inter-component correlation group comparisons

When repeating the analyses using the extended database from longitudinal data, new and similar results emerged.

A group effect was revealed on the FC between the bCEN and gDMN, showing that BpO and SzO exhibited slightly higher mean connectivity when compared to HC. As

explained in the introduction, the CEN and DMN should work in an anticorrelated switch, which is achieved along neurodevelopment, when the networks turn into more effective functional domains (segregation) and the communication between them is better regulated (SN as a mediator). Our results support poorer segregation of the two networks, since the CEN and DMN show higher values of inter-network connectivity in our FHR sample compared with HC.

This effect was maintained when examining the direct effect of age on these findings, which showed a positive relationship with age in the SzO group compared to the HC. This is consistent with our cross-sectional results and with the literature, which suggests a weaker segregation of these networks with age. In fact, studies with psychotic patients revealed that increased FC between DMN and CEN was related with psychotic symptoms severity [85].

Moreover, a previous finding regarding the CEN is replicated with longitudinal data. The right and left components of this network decrease their connectivity along age, showing a disconnectivity trend in SzO group in comparison with controls. Again, this suggests weaker integration of this network, which has suggested to underpin executive functioning which is a core feature of psychotic disorders [85].

To conclude this section, it is important to emphasize that while statistical significance alone is not sufficient to establish definitive conclusions in this study, the observed dynamics in the networks that exhibited effects prior to multiple comparisons correction appear to be consistent with the existing literature and recent findings in studies of FC in RSNs. These provide valuable insights into the potential alterations in FC associated with risk factors for mental health disorders. However, further research is warranted to validate and expand upon these preliminary results, considering the complexity and multifaceted nature of the neurobiological mechanisms underlying psychiatric conditions.

5.1 Limitations and future work

Along the development of this study, two main categories of limitations could be addressed as relevant.

First and foremost, I would like to address the methodological and resource limitations that we encountered during the course of this research, which had a notable impact on the execution of the methodology. The major limitation was the occurrence of a cyber-attack at the Hospital Clinic, which resulted in a significant disruption of resources, including the loss of internet connection. This disruption persisted for an extended period, overlapping with the duration of this study. Moreover, as the analysis involved patient information, it was not possible to continue from a remote location. Although this event occurred after gaining access to the BSC, which allowed us to proceed with the processing, the cyber-attack hindered significantly the image processing workflow by the lack of internet connectivity at the center.

Secondly, several limitations involving data characterization and availability should be considered in future research to improve the understanding of these analyses. It is

crucial to adopt a more comprehensive perspective on the objectives of exploratory studies, with a focus on translating relevant findings into clinical applications.

Within this section, the main limitation is the heterogeneity of the sample, as the classification may lack clinical variables to address cognitive levels. Previous studies have demonstrated the presence of different phenotypes within HR cohorts, exhibiting varying levels of FC according to the manifestation of symptoms. To overcome this limitation, future research should consider correlating FC findings with clinical information, such as depression, mania, and psycho-social functioning scores, but also with cognitive performance, to assess the impact of connectivity differences on the phenotype. Longitudinal studies integrating clinical assessments can investigate whether distinct neurodevelopmental sub-groups can be clustered based on functional changes over time and whether these changes can be predicted by baseline characteristics. Furthermore, if we consider the hypothesis of a continuum of different mental disorders and the increased risk of SzO and BpO individuals developing other pathologies, it is essential to assess psychiatric comorbidities. Additionally, it is worth noting that some offspring participants in the study undergo clinical assessment and receive psychotropic medication to control and prevent psychiatric outcomes. This has been proven to induce changes in the FC, which is a factor that may introduce errors or confound the FC analysis since these data were not available to use as covariates.

Overcoming these limitations requires the acquisition of significant clinical assessment information and variables to enhance sample characterization. This will allow a more effective translation of research findings into clinical practice.

Second, several additional limitations should be considered in the interpretation of the findings. First, the availability of acquisitions during the follow-up period varied, with some FHR patients displaying lower attendance. This discrepancy in data availability may introduce a potential bias, as the participants who remained in the study throughout the follow-up period could represent a selected sample, possibly biased towards individuals with better overall condition and mental state. Moreover, the original dataset underwent a significant reduction after QC procedures, which further reduced the sample size. The sample size could have potentially limited the statistical power to detect significant differences.

Third, regarding the methodological workflow, it is important to acknowledge a limitation associated with the identification of RSNs using a parcellation template based on adult findings. While this approach ensures consistency in comparing the same regions, it fails to account for inter-individual and age-related variations in the topography of RSNs. To address this limitation, future studies can employ more personalized parcellations that capture individual differences in network organization.

Additionally, it is important to acknowledge that the RSNs were studied based on the temporal correlation of whole ICs derived from a simple parcellation consisting of 20 ICs. This approach may limit the ability to identify distinct functional domains within each network. To address this limitation, future research could employ a larger number of ICs during the independent component analysis (ICA), allowing

for more fine-grained network fragmentation and characterization.

The last limitation is about noting that only linear relationships between FC and age were investigated in this study. While this choice reduces the risk of overfitting, it may oversimplify the complex neurodevelopmental changes that occur during adolescence. Cognitive and brain development do not always exhibit linear trajectories. Future investigations could consider incorporating non-linear modeling approaches to capture the dynamic and nonlinear nature of brain processes and reflect it in the FC development.

Finally, it is obvious that the field of psychosis research faces challenges in translating fMRI findings into clinical applications due to the complexity and variability of protocols and conclusions. The incorporation of standardized methods, as employed in this thesis, is crucial in overcoming these challenges and facilitating homogeneity for robustness and clinical translation.

Overall, this research has focused on studying FC of RSNs in a FHR cohort, during an important period in brain development. The identified limitations serve as valuable insights, driving future research towards greater precision. These limitations provide motivation for further refinement and exploration, ultimately contributing to a more comprehensive understanding of the underlying mechanisms of psychosis development.

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