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SURFACE-BASED MORPHOMETRY AND CORTICAL COMPLEXITY: FROM PSYCHIATRIC DISORDERS TO COGNITION AND BEHAVIOR

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Abstract

This thesis aims at investigating cortical surface measures, specifically cortical complexity, and their importance on the understanding of psychiatric disorders, behavior and cognition. We performed three different studies to reach this goal. In Study 1, we aimed to investigate the brain cortical alterations underlying bipolar-schizophrenic spectrum disorders: patients with schizophrenia, patients with bipolar disorder, and healthy subjects were compared investigating SBM based cortical complexity measures (fractal dimension). Then, we proposed to correlate such structural abnormalities with available clinical and cognitive measures. Cortical complexity was reduced in schizophrenia patients compared to healthy controls in the right superior temporal gyrus while bipolar disorder patients showed significantly lower cortical complexity in the left pars opercularis compared to healthy controls. Additionally, bipolar patients had increased cortical complexity in the left lingual gyrus and this measure was positively correlated with the severity of manic symptoms. When compared to schizophrenia, bipolar patients showed significant increases in cortical complexity in the left inferior temporal gyrus, right temporal pole, inferior and superior temporal cortex. In Study 2, the objective was to investigate cortical complexity in patients with cocaine addiction. Since the frontal, parietal, temporal and insular cortices have been shown to play an important role in decision making and impulsivity, we hypothesized that cortical complexity in the brain of patients with cocaine addiction would be altered in these regions. Moreover, impulsivity is commonly associated with cocaine and the development to its addiction, so we expect that these alteration in the cortical surface may be related to measure of impulsiveness. The results showed that patients with cocaine addiction had higher levels of impulsivity and reduced cortical complexity in a cluster encompassing the left insula and supramarginal gyrus, as well as in the left medial orbitofrontal cortex. Additionally, the cortical complexity in the left medial

orbitofrontal cortex was correlated with the age of onset of cocaine addiction and with attentional impulsivity. These findings do indeed suggest that chronic cocaine use may be associated with changes in the cortical surface in fronto-parieto-limbic regions involved in emotional regulation, and that these changes may be linked to earlier use of cocaine. Finally, in study 3, our objective was to investigate changes in the brain surface of chess experts using cortical complexity and gyrification measures. We hypothesized that the surface indexes of the brain regions and networks underlying high-order cognition, including fluid intelligence, working memory, processing speed, and visuospatial processing, namely, prefronto-parieto-temporal networks, would be altered. Additionally, since training in the chess game usually starts during childhood, we hypothesized that these indexes would be correlated with the training time of chess practice. The results showed that in chess experts, the cortical complexity was increased in the left frontal operculum and correlated with the starting age of chess practice, and decreased in the right superior parietal lobule. Chess expertise, also investigated through a logistic regression model was indeed predicted by the cortical complexity in a network of fronto-parieto-temporal regions. These findings suggest that the complex properties of the brain surface in a network of transmodal association areas important for flexible high-level cognitive functions are important for chess expertise, and that these changes may develop over time with long-lasting practice.

Chapter 1

1. Introduction

1.1 The brain and its structure

One of the earliest systematic studies of the human brain, which took place in half a century ago, sparked curiosity about the relationship between brain structure and function, as well as the impact of brain folding on abilities (Richman et al., 1975). Since then, more studies focused their effort on understanding the patterns and the structures of our brain. Over the course of human evolution, as well as during the development of individuals, the enlargement of the brain is directly associated with an enhancement of intellectual capabilities (Hofman, M. A. 1989). Due to the unique shape of each individual brain, especially for larger species, nonlinear registration techniques are essential for comparing the different brain structures (Ashburner & Friston, 2000). Early development can result in the formation of population- and disease-specific patterns in addition to highly individual pattern folding (Tallinen et al., 2016). The brain is made up of two main types of tissue: gray matter (GM), which is the processing region containing a large number of neurons connected by myelinated dendrites that form white matter fiber tracts and enable high-speed communication between different regions, and white matter (WM), which is composed of these fiber tracts. The brain is also surrounded by cerebrospinal fluid (CSF) and housed within the skull. The cerebrospinal fluid acts as a physical buffer that enables geometrical changes in brain development and aging. The folding of the cortex, a ribbon of gray matter surrounding white matter, allows it to fit compactly within the cranium. This organized surface is particularly enlarged during individual and evolutionary development (Budday et al., 2015). The neocortex, which is the cortex of the cerebrum, is organized into six layers with regional variation in thickness and different functional

processing. Its structure is further influenced by the local folding and compensates for the number of layer-specific neurons (Amunts & Zilles, 2015). For example, a cortical unit located on the top of a gyrus has a larger outer surface area and a smaller inner surface area, with a thicker inner layer and a thinner outer layer. On the other hand, a cortical unit located on the bottom of a sulcus has a smaller outer surface area and a larger inner surface area, with a thicker outer layer and a thinner inner layer. It is believed that local folding has only a limited impact on function and may be seen as the result of energy-minimizing processes related to brain growth (Amunts & Zilles, 2015). Magnetic resonance imaging (MRI) and automatic preprocessing techniques allow for the in vivo analysis of the macroscopic brain structure in the field of computational morphometry, even in large cohorts. Early regional manual measures have been extended to automatic whole brain techniques such as voxel-based morphometry (VBM), region-based morphometry (RBM), deformation-based morphometry (DBM), and surface-based morphometry (SBM). SBM allows for significant improvements compared to VBM or DBM by providing additional measures that describe the shape of the brain, allowing for the dissection of GM volume into thickness and other measures, improving registration and partitioning, correct anatomical smoothing, mathematical shape modeling, and the combination of different MRI modalities such as functional imaging, diffusion imaging, and structural weightings. Over the years, the volume of the GM and the cortical thickness have become important biomarkers for development, aging, plasticity, and various diseases (Shen & Chung, 2006).

Although VBM is sensitive to subtle GM changes in the brain, it lacks the function to describe complex folding patterns and their development. DBM, on the other hand, partially covers folding differences as well as volume changes that impede analysis. RBM allows the combination of different techniques but highly depends on the atlas maps.

1.2 Brain development, plasticity and aging

The development of the cerebrum in mammals goes through three main stages: ballooning, gyrification, and scaling. The ballooning phase involves the expansion of the ventricle, which compensates for the tangential growth of the intermediate zone and increases the surface area of the brain without significant folding. The gyrification phase is characterized by the formation of specific structures, such as the central sulcus, and is influenced by internal forces in the white matter or tangential growth in the gray matter. The scaling phase occurs in childhood and adolescence and involves a balance between tangential and radial growth. Changes in the adult brain, such as plasticity and aging, also affect the structure of the brain. Larger brains tend to have more individualized folding patterns due to higher tangential growth compared to radial growth (Budday et al., 2015).

During the first few weeks of human gestation, the brain undergoes an intensive period of expansion. This is characterized by an increase in the size of the ventricle, accompanied by the growth of the intermediate zone and the brain's surface. During this time, only a few fissures become prominent due to bending. Neurons are produced in the ventricular zone and migrate to the skull, where they contribute to the development of the cortical layer. At this stage, the cortex exhibits a radial pattern on diffusion MRI, which indicates low connectivity within the cortex. Additionally, the first large fiber tracts become visible in the white matter (Huang, 2010).

During the gyrification process, which occurs after the ballooning phase, it is believed that the internal forces of WM connectivity or tangential growth of GM play a role in the formation of cortical folds. External forces, such as those caused by the constraints of the skull and meninges, have been found to have a minor effect (Bayly et al., 2014). Recent experimental and computational growth models suggest that the natural folding of the brain is a result of an energy-minimizing process of surface expansion that is influenced by the stiffness of the inner core, the growing rate, and local thickness. Thinner regions and faster growing rates tend to

lead to more folding, while stiffer cores may result in more complex structures (Bayly et al., 2014).

The process of folding in the human brain is typically completed around the time of birth, at which point both radial and tangential growth are balanced again (Evans, 2006).

Throughout an individual's lifetime, the cortex, steadily but very slowly, shrinks each year, while the WM continues to grow up until around age of 40. The WM may also show degeneration, as evidenced by MRI as WM hyperintensity with GM-like intensities in aging and in diseases such as multiple sclerosis. In addition to global tissue atrophy, brain plasticity allows for an increase in local tissue volume. For elderly individuals and people with neurodegenerative diseases such as Alzheimer's disease, accelerated tissue atrophy has been observed (Ziegler et al., 2014). Overall, tissue atrophy is accompanied by an enlargement of the ventricle and sulcal CSF, which maintains the general shape of the brain within the skull.

1.3 The study of the brain surface

Surface-based analysis of MRI images has been a popular approach for studying the development of the brain as an organized surface. This has resulted in the development of several software packages for automatic surface reconstruction and analysis. Surface meshes are graph structures that describe a shape by a set of vertices and faces connecting the vertices. Surface measures, which are stored as vertex or face-wise vectors, can be visualized as surface textures and analyzed using techniques similar to VBM. These measures can be generated on a regular volume grid using algorithms like marching cubes or isosurface methods, but they usually require additional pre- and post-processing. The quality of the generated meshes and measures depends on the method used, the structure being reconstructed, and the quality of the input data. In general, structural data that is suitable for VBM analysis can also be used for SBM analysis.

Preprocessing using voxel-based techniques is necessary to map individual brains to common templates, classify different tissues, and prepare data for surface reconstruction. Classification of WM, GM, and CSF is based on image intensity and priors, and typically involves brain-extraction, handling of image interference such as noise and inhomogeneity, and registration (Ashburner & Friston, 2005). To improve accuracy and stability, recent approaches use brain-specific properties such as topological constraints, multiple input images, longitudinal modeling, templates and parameters specific to species or aging, or other concepts. Segmentation can also be used to normalize MRI intensities (Ashburner & Friston, 2005). Spatial registration involves estimating a mapping between an individual brain and common templates, often through iterative processes starting with affine transformations and low-frequency deformations that are gradually increased to reduce anatomical variance among subjects. Atlas maps that divide brains into different regions are often obtained in the native space and mapped to an average template space, or directly generated in the template space (Ou et al., 2014).

Shape analysis requires surfaces with identical topology, which can be achieved in two ways. The first approach is to use an existing template mesh and deform it to fit the individual anatomy, which works well for simple, unfolded structures but can be problematic for strongly folded ones. The second approach, known as bottom-up methods, involves creating an individual object and registering it to an average mesh, typically a sphere (Tosun et al., 2004). When reconstructing the neocortex of both cerebral hemispheres, most methods use the GM-WM surface, as it provides a better initial representation of the folded brain than the GM-CSF boundary, which can be blurry in sulcal regions (Eskildsen & Østergaard, 2006). Other methods use the central surface, which runs through the middle of the cortex and is the average of the inner and outer surfaces and is therefore less noisy (Dahnke et al., 2013). In order to analyze shape, the surface mesh must be deformed to the CSF-GM boundary to estimate the cortical thickness, while also having to optimize and fixing the topology of the mesh.

Modification of said meshes is essential to optimize them, preparing the surface registration and creating modified meshes optimized to specific shape measures. Smoothing averages the coordinates of each vertex with its neighbors and removes artifacts but also anatomical details. Deformation moves the vertices based on internal forces (mesh connectivity) and external forces (tissue intensities). Remeshing (refinement/repair) alters the complexity and the topology of the mesh. Parameterization involves the analysis and synthesis of signals using simpler trigonometric functions. Averaging mixes normalized meshes with different vertex locations but identical structures to create a common mesh.

Surface registration is the process of aligning the structures of individual brains through the minimization of surface properties and shape features. It is used to compare individual meshes by mapping them to a common template, such as a sphere. Surface registration can be applied to small (intra-individual), medium (inter-individual), or large (inter-species) folding patterns. While voxel-based registration is accurate, surface-based registration benefits from the improved characterization of the cortex through surface measures and advanced alignment of individual structures (Van Essen et al., 2001).

1.4 Surface-Based Morphometry (SBM)

Surface analysis has become an important aspect of structural brain imaging. Like VBM, SBM can be evaluated globally, by regions, or continuously over the entire surface. In addition to these capabilities, SBM also allows for more subtle measures, anatomical correct registration and smoothing, and direct interaction with mathematical folding models. In layman's terms, SBM allow to provide answers that VBM cannot reach.

SBM has several drawbacks, including high complexity which can make it vulnerable to noise, artifacts, and errors, as well as significant computational demands. Also, the interpretation of some folding measures can also be complex. Surface preprocessing, which is more complex and therefore more prone to errors, may also be less sensitive and less robust, especially for subtle changes in brain plasticity. However, constraints can improve robustness and the

increased complexity of SBM allows for more characteristic measures, advanced anatomical registration and smoothing, which may compensate for these drawbacks.

To understand the causes and effects of individual and evolutionary folding development, surface properties are key factors. Surface analysis offers a wide range of new or improved measures with various definitions and properties that require careful evaluation, particularly for abstract shape measures.

There are several different types of surface-based morphometry techniques that have been developed and applied in neuroimaging research. Some of the most commonly used techniques include cortical thickness, gyrification index, and cortical complexity.

Cortical Thickness

Cortical thickness refers to the distance between the pial surface and the white matter surface of the cerebral cortex, which is the outer layer of the brain responsible for higher cognitive functions such as perception, attention, and memory. It is an important measure of brain development and structure and has been widely studied in both healthy individuals and those with neurodevelopmental and neurodegenerative disorders (Ashburner & Friston, 2005).

Cortical thickness is known to vary across different brain regions and across different age groups. It is generally thicker in the primary sensory and motor cortices and thinner in the association cortices. It also tends to be thicker in children compared to adults, with a peak in thickness during the early developmental years and a gradual decline during adolescence and adulthood (Madre et al., 2020).

There are several factors that can influence cortical thickness, including genetics, environmental influences, and brain connectivity. Studies have shown that genetics plays a significant role in determining cortical thickness, with heritability estimates ranging from 40% to 80%. Environmental factors such as prenatal exposures, childhood experiences, and lifestyle factors can also affect cortical thickness. Finally, brain connectivity, or the strength and pattern of connections between different brain regions, can influence cortical thickness by

affecting the amount of information processing and communication that occurs in different brain regions (Suh et al., 2019).

Abnormalities in cortical thickness have been associated with various neurodevelopmental and neurodegenerative disorders. For example, studies have shown that in individuals with bipolar disorders, the majority of studies reported thinner cortical thickness in the left anterior cingulate cortex and the left superior temporal gyrus, as well as several prefrontal regions. Similar investigations also show consistency of cortical thinning in individuals with bipolar disorder and schizophrenic patients in temporal and frontal regions, suggesting a common neuropathology (Hanford et al., 2016).

Gyrification Index

The gyrification index is a measure of the degree of folding or convolution of the cerebral cortex and is calculated by estimating the ratio between the total and the superficially exposed cortical surface of the brain (Zilles et al., 1988). The cerebral cortex exhibits individual and regional differences in gyrification, which are influenced by factors such as the forces that drive the extensive cortico-cortical connections along the brain surface and the fundamental principles of cortical development and organization. During fetal development, the cortex undergoes significant increases in gyrification. After the brain reaches approximately half of its final volume, gross folding patterns become stable (Zilles et al., 1988). There are two main hypotheses for the process of cortical gyrification: the gray matter hypothesis and the mechanical tension hypothesis. The gray matter hypothesis suggests that regional cortical gyrification is caused by growth processes during cortical development, such as neuronal differentiation and migration. These processes establish a foundation for subsequent changes in gyrification that may occur during childhood, adolescence, and adulthood. The mechanical tension hypothesis proposes that underlying intracortical axonal connections influence gyrification. Brain regions with greater neural connectivity have higher tension, which allows these regions to remain closer together during brain growth, leading to the formation of gyri.

Changes in neural connectivity, such as those that occur during synaptic pruning and dendritic arborization, could potentially alter the shape of gyri and sulci (Garcia et al., 2018).

The gyrification index has been found to vary among individuals and across different brain regions and has been associated with a range of clinical and cognitive traits. For example, higher gyrification has been linked to higher intelligence, better cognitive performance, and a lower risk of neurological and psychiatric disorders (L. Li et al., 2021). In schizophrenia, several studies appointed deficits in gyrification in frontal and temporal regions. Remarkably, these abnormal gyrification characteristics could also be observed, even though at an inferior level, in first-degrees relatives (Matsuda & Ohi, 2018).

Cortical Complexity

In recent years, there have been important changes in development of novel methodological tools in the study of the brain cortex. The most promising index is the fractal dimension (FD), a measure that has been previously used to investigate natural structures and their complexity (Mandelbrot, 1967) and that has been applied across multiple scales, from the molecular level to the whole brain (Di Ieva et al., 2015).

FD is a measure that characterizes the complexity of an object across different spatial scales. It provides a numerical value that reflects the self-similarity of a structure or its overall complexity. Using fractal geometry tools, the complex geometry of GM can be examined because of the fractal properties resulting from the recurrence of convolution patterns.

Different methods can be applied to investigate said cortical complexity. One example is the box counting algorithm. In this procedure, which is designed to estimate the space-filling property of an object regardless of whether it is a fractal or not (Madan & Kensinger, 2016), by calculating regional areas for progressively lower sampling resolutions. Since the number of vertices continually decreases, the position of said vertices can have an important impact on the FD measure and could overlook essential cortical complexity information. One way to overcome these difficulties is by aligning sulci across the subjects to the same cortical

coordinates for each vertex for all subjects. However, these procedures is complicated and requires often manual delineation of geometrically corresponding areas across the subjects. Another method, useful to extract cortical complexity information, is the spherical harmonic (SPH). Using SPH reconstructions allows for the number of vertices to remain constant across all reconstructed surfaces, which minimizes the impact of individual vertex alignment and avoids the need for re-gridding the surface, which can introduce error through interpolation. Additionally, examining the pattern of regional differences in structural characteristics, rather than relying on a single global metric, may be more effective in analyzing clinical disorders (Yotter et al., 2011a). This method has the advantage of using data from multiple brain regions to create a unique neuroanatomical signature. This can be useful in research on mental illnesses such as schizophrenia (Yotter et al., 2011a). By utilizing SPH-derived reconstructions, it is possible to calculate a local FD for each vertex in the reconstruction. This is a crucial first step in establishing accurate neuroanatomical signatures for different disease states. Additionally, a comparison of the test-retest reliability of three FD estimation algorithms found that the spherical harmonic reconstructions had the highest intraclass correlation of surface-based estimations. Furthermore, FD was found to be more consistent and less affected by head motion than other morphological measures such as cortical thickness and gyrification (Madan & Kensinger, 2016).

The relationship between FD and other measures of the cortical surface has been investigated in several studies. For example, It was observed that FD had a positive correlation with the folding area (FA) and a negative correlation with the cortical thickness in both hemispheres (Im et al., 2006). On the other hand, Madan and Kensinger (2016) found a positive relationship between whole-brain FD and cortical thickness. Two studies have examined the relationship between FD and the GI with conflicting results. (Madan & Kensinger, 2016) found a positive correlation, while (Lu, 2020) found a negative correlation between the GI and the FD of the left dorsolateral prefrontal cortex (DLPFC).

(Nenadic et al., 2014) divided a sample of schizophrenia patients into three subgroups based on predominantly negative, disorganized, or paranoid symptoms. They found that the negative

subgroup had reduced FD in the right hemisphere and in specific regions in the left hemisphere, including the caudal anterior cingulate, precentral, and superior frontal regions. The paranoid subgroup had reduced FD in the right hemisphere and in the right superior parietal lobe, while the disorganized group did not show any differences in FD measures compared to the healthy control group. (Wolf et al., 2021) compared cortical complexity in two groups of schizophrenia patients, one with and one without parkinsonism. They found that patients with parkinsonism had increased cortical complexity in the left supplementary motor cortex compared to those without parkinsonism. (Nenadic et al., 2017)used spherical harmonic reconstruction to estimate FD in bipolar patients and found increased FD in the left lateral orbitofrontal cortex and right precuneus, as well as decreased FD in the right caudal middle frontal, right entorhinal cortex, right pars orbitalis, left fusiform cortex, and left posterior cingulate cortex. Cortical complexity play an important role also on human cognition. (Im et al., 2006) found a positive correlation between FD of the whole brain and years of education, as well as between FD of the right hemisphere and IQ in a sample of healthy young adults. (H. Liu et al., 2020) studied the relationship between FD and cognition in older individuals (ages 70-90) and found significant correlations between FD and global cognition in the bilateral temporal lobe, left occipital lobe, and several subcortical structures. Cortical complexity and FD, its associated measure, seems to be a strong and promising method on analyzing cortical surface structure in psychiatric and neurological disorders.

1.5 Scientific Proposal

This thesis aims at investigating cortical surface measures, especially cortical complexity, and their importance on the understanding of psychiatric disorders and cognition. To reach this goal, three separate study have been conducted.

In Study 1, we aimed to investigate the brain cortical alterations underlying bipolar-schizophrenic spectrum disorders: patients with schizophrenia, patients with bipolar disorder, and healthy subjects were compared investigating SBM based cortical complexity measures (fractal dimension). Then, we proposed to correlate such structural abnormalities with available clinical and cognitive measures.

In Study 2, the objective was to investigate cortical complexity in patients with cocaine addiction. Since the frontal, parietal, temporal and insular cortices have been shown to play an important role in decision making and impulsivity, we hypothesised that CC in the brain of patients with cocaine addiction would be altered in these regions. Moreover, impulsivity is commonly associated with cocaine and the development to its addiction, with cocaine addicts usually showing higher scores on the BIS-11 scale when compared to healthy controls. Indeed, we predicted the association between CC changes and 1) the duration of cocaine use for its widespread neurotoxic effects and 2) impulsivity characteristics (in particular, for the attentive subdomain) in those regions implicated in the predisposition to addiction.

In Study 3, our objective was to investigate changes in the brain surface of chess experts using cortical complexity and gyrification measures. We hypothesized that the surface indexes of the brain regions and networks underlying high-order cognition, including fluid intelligence, working memory, processing speed, and visuospatial processing, namely, prefronto-parieto-temporal networks, would be altered. Finally, since training in the chess game usually starts during childhood, we hypothesized that these indexes would be correlated with the training time of chess practice.

Chapter 2

2. Study 1: Cortical folding complexity is distinctively altered in schizophrenia and bipolar disorder

The contents of this study have been published in Schizophrenia Research (Trevisan, Miola, et al., 2022):

Trevisan N, Miola A, Cattarinussi G, Kubera KM, Hirjak D, Wolf RC, Sambataro F. Cortical folding complexity is distinctively altered in schizophrenia and bipolar disorder. Schizophr Res. 2022 Mar;241:92-93. doi: 10.1016/j.schres.2022.01.037. Epub 2022 Jan 29.

2.1 Background

The Kraepelinian dichotomy between schizophrenia (SZ) and bipolar disorder (BD) remains still controversial, and continues to be debated given disputed boundaries, weak diagnostic validity, and limited promise for biological significance (d'Albis & Houenou, 2015). Growing evidence revealed that genetic risk is partly shared between schizophrenia and bipolar disorder (Cardno et al., 2002). Moreover, SZ and BD share environmental contributions, including prenatal factors (Brown et al., 2000), childhood adversity (Matheson et al., 2013), substance misuse (Henquet et al., 2006) and urbanicity (Heinz et al., 2013). Moreover, several clinical features show a significant overlap between SZ and BD, including alterations of thought, perception, cognition, emotion and behavior (Murray et al., 2004). Patients with SZ frequently present with depressive symptoms (Häfner et al., 1999), conversely, 55 and 90% patients with BP show psychotic symptoms. Additionally, schizophrenic and bipolar disorder patients (during both syndromic mood disturbance and remission) share impairments in many cognitive domains, including attention, memory, and executive functions (Daban et al., 2006)

as well as alterations in affective processing (Gopin et al., 2011). Due to all these overlapping clinical and neuropsychological impairments, it can be challenging to differentiate the two disorders, especially in the first stages of the illness. Moreover, empirical efforts to identify a more fundamental, transdiagnostic phenotype of psychosis at the clinical symptom level remain remarkably limited (Reininghaus et al., 2016).

The identification of diagnosis-specific biomarkers, including brain imaging can help the clinician to differentiate schizophrenia and bipolar disorders and provide more tailored treatments (Rapoport et al., 2012). A meta-analysis of VBM studies has revealed that schizophrenic patients were characterized by extensive grey matter deficits in frontal, temporal, cingulate and insular cortex and thalamus, and increased grey matter in the basal ganglia. (Ellison-Wright & Bullmore, 2010a) Bipolar patients showed grey matter reductions in the anterior cingulate and bilateral insula (Ellison-Wright & Bullmore, 2010b). Another VBM meta-analysis, although with a smaller sample size, revealed substantial overlaps in the regions affected by schizophrenia and bipolar disorder included regions in prefrontal cortex, thalamus, left caudate, left medial temporal lobe, and right insula (Yu et al., 2010). Notably, GM reductions are typically more extensive in SZ than in BD patients even when SZ studies are selected to match the mean age of onset and illness duration of BD studies (Ellison-Wright & Bullmore, 2010b). Notwithstanding some well documented trans-diagnostic differences (Redlich et al., 2014), there is also considerable overlap of brain structural volumetric abnormalities seen in BP compared to unipolar depression (Wise et al., 2017), to SZ (Maggioni et al., 2016) and other psychiatric disorders, (Goodkind et al., 2015) pointing to the problem of specificity of findings (Nenadic et al., 2017).

A technique to investigate additional brain features is the surface-based morphometry (SBM), that enables to analyze features such as cortical thickness, gyrification and complexity .
Given the observation that the cortical folding tends to develop until early childhood and then remains stable for much of the life-span, cortical gyrification has been suggested as a way to

investigate endophenotype in schizophrenia and bipolar disorders, as it is more specifically determined by neurodevelopmental and genetic factors (Yotter et al., 2011a).

Another way to analyze the cerebral cortex is offered by fractal geometry (Kiselev et al., 2003), a novel spherical-harmonics based approach which is optimally designed for the analysis of complex morphological patterns (Collantoni et al., 2020).

Cortical complexity, similar to gyrification, is an inherent morphometric feature that is more temporally stable (Yotter et al., 2011a) than volume or VBM-derived measures of grey matter. Studies directly comparing gyrification patterns between schizophrenia and bipolar disorder are scarce and still controversial (Madre et al., 2020), and to the best of our knowledge, abnormalities in cortical complexity have yet to be investigated among bipolar-schizophrenic spectrum.

Thus, we aimed to investigate the brain cortical alterations underlying bipolar-schizophrenic spectrum disorders. Specifically, 43 patients with schizophrenia, 47 patients with bipolar disorder, and 65 healthy subjects were compared investigating SBM based cortical complexity measures (fractal dimension). Then, we proposed to correlate such structural abnormalities with available clinical and cognitive measures.

2.2 Materials and methods

2.2.1 Participants

Patients with SCZ, BD, and healthy controls (HC) were selected from the Consortium for Neuropsychiatric Phenomics dataset. This dataset contains scans from 272 right-handed subjects, with a minimum of 8 years of completed formal education. Subjects were recruited by reaching out to local clinics and online portals. Patients with psychiatric comorbidities were excluded. From the original database, we excluded individuals with mild head injury (with loss of consciousness for a time between 2 to 30 minutes), current medical illness, past or current

substance abuse and/or dependence, past major depressive disorder, anxiety disorders, and ADHD. Furthermore, HCs were excluded if they had any past or current diagnosis of psychiatric disorder. The final sample included 43 patients with SCZ, 47 patients with BD type-1 in partial or full remission, and 65 HCs (Table 1).

Clinical assessment was performed using the Brief Psychiatric Rating Scale (BPRS) for psychiatric assessment, the Hamilton Rating Scale for Depression (HAM-D), the Young Mania Rating Scale (YMRS) for the evaluation of the mood symptoms, and the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS) to measure psychotic symptoms. Information about current psychiatric medications was recorded for all patients. The treatment dosage for each drug class (i.e., antipsychotics, mood stabilizers, antidepressants) was transformed to defined daily doses of drug intake (DDD) ratios as described by the World Health Organization Collaborating Centre for Drug Statistics Methodology System of Defined Daily Doses.

Characteristics	BP (N=47)	SZ (N=43)	HC (N=65)	F or χ	P
Demographics					
Age (Y), mean ± SD	35.3 ± 8.9	35.7 ± 8.7	33.1 ± 8.8	1.417	0.248
Females, n (%)	19 (40.4)	13 (30.2)	34 (79.1)	3.87	0.144
Education, mean ± SD	14.53 ± 1.9	12.46 ± 1.6	15.00 ± 1.8	28.87	<0.001 [b, c]
Clinical					
HAMD, mean ± SD	14.0 ± 9.8	11.6 ± 9.3		1.2	0.233
YMRS, mean ± SD	12.2 ± 11.0	8.1 ± 6.9		2.1	0.039 [c]
SANS, mean ± SD	5.83 ± 3.6	9.37±4.8		-4.44	<0.001 [c]
SAPS, mean ± SD	2.37 ± 2.3	7.11±4.3		-6.38	<0.001 [c]
BPRS, mean ± SD	7.76±2.0	8.75±2.6		-2.0	0.048 [c]
Current pharmacotherapy					
Antidepressants, n (%)	15 (31.9%)	22 (51.1%)		-0.533	0.595
Antidepressant dose (DDD)	0.53±0.9	0.62±1.0		-0.395	0.693
Antipsychotics, n (%)	26 (55.3%)	36 (83.7%)		3.709	<0.001 [c]
Antipsychotic dose (DDD)	0.53±0.6	0.17±0.2		3.668	<0.001
Mood Stabilizers, n (%)	34 (72.3%)	10 (23.3%)		-1.976	0.051
Mood Stabilizer dose (DDD)	0.84±2.1	2.07±3.7		-1.893	0.061

Table 1. *Sociodemographic and clinical characteristics of the sample.* [a, b, c] *p<0.05 Tukey post-hoc for BP vs HC, SZ vs HC, BP vs SZ contrasts, respectively.*

2.2.2 Brain imaging

Imaging acquisition. MRI data were acquired on a 3T Siemens Trio scanner using T1-weighted high-resolution anatomical scans (MPRAGE) with the following parameters: TR=1.9 s, TE=2.26 ms, FOV=250 mm, matrix =256 × 256, sagittal plane, slice thickness=1 mm, 176 slices.

Preprocessing. We used the Statistical Parametric Mapping analysis package (SPM12) together with the Computational Anatomy Toolbox for SPM (CAT12) with the standard protocol (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). Briefly, T1 images were spatially registered to the Montreal Neurological Institute (MNI) template using DARTEL registration (Ashburner, 2007). Brain structural data were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and then used for the reconstruction of the cortical surface for each participant using the projection-based thickness method (Dahnke et al., 2013). The central surface reconstruction included topology correction, spherical inflation, and spherical registration. The central surface was used as the input for calculating the gyrification index, the fractal dimension, and sulcal depth values. Finally, all surface measures for both hemispheres were merged and resampled to a 32k mesh resolution. We also included a two-step quality check: first, all images were inspected visually for artifacts before the pre-processing. Then, after segmentation, the images underwent a quality control for intersubject homogeneity and image quality as included in the CAT12 toolbox, which uses noise contrast, inhomogeneity contrast, and root mean square of voxel resolution. None of the subjects was excluded for artifacts.

Cortical Complexity estimation and comparison. CC was analyzed as in Dahnke et al. (2013)(Dahnke et al., 2013a), using a spherical harmonic reconstruction approach(Yotter et

al., 2011). Briefly, for each vertex, the spherical harmonics coefficient was extracted with maximum degrees (*l*-value) ranging from 11 through 29 and remapped into the harmonic space using a modified Fast Fourier transform. CC was calculated as the slope of the linear portion of the regression of the log (area) relative to the maximum *l*-value. Local CC was then re-parametrized in a common coordinate system using the *fsaverage* spherical mesh included in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). Resampled surface data for Fractal Dimension values were smoothed using a 25 mm (and 20 mm) Gaussian Full Width at Half Maximum (FWHM) prior to 2nd level analysis. Local whole-brain CC was compared using a one-way ANCOVA with diagnosis as a predictor and age as a covariate. Statistical significance was based on a family-wise error (FWE) corrected cluster-level threshold of $p<0.05$.

2.2.3 Statistical analysis

Demographic, clinical, and pharmacotherapy data were compared across diagnostic groups using chi-square tests for categorical variables and one-way ANOVA for continuous variables followed by pairwise chi-square/Tukey post hoc comparisons, respectively. The normality of the data distribution was assessed through a Kolmogorov-Smirnov test. Due to the distribution of the variables, we used Pearson's correlation to investigate brain-behavior correlations and Spearman's correlation to investigate brain-drug treatment associations for each drug class. The level of significance was set to $p<0.05$ for all tests. Data analysis was performed with Jamovi (Version 1.2, https://www.jamovi.org) and R (http://www.rstudio.com/).

2.3 Results

2.3.1 Cortical Complexity

CC was reduced in SCZ compared to HC in the right superior temporal gyrus (STG, x,y,z=42, 15, -18; k=189, p=0.035). BD displayed significantly lower CC in the left pars opercularis

(x,y,z= -54,9,23; k=164; p=0.05) along with increased CC in the left lingual gyrus (x,y,z=10, -71, 1; k=179; p=0.041) relative to HC. When compared to SCZ, BD showed a significant CC increase in the left inferior temporal gyrus (x,y,z=-50, -44, -11; k=241; p=0.014), the left lingual gyrus (x,y,z= -9, -77, 2; k=236; p=0.015), the right STG (x,y,z= 59, -9, -5; k=175; p=0.045), and in the right temporal gyrus (x,y,z= 40, 15, -19; k=261; p=0.009) (Fig. 1). No significant correlations were found between cortical complexity values and antipsychotic, antidepressant and mood stabilizers use.

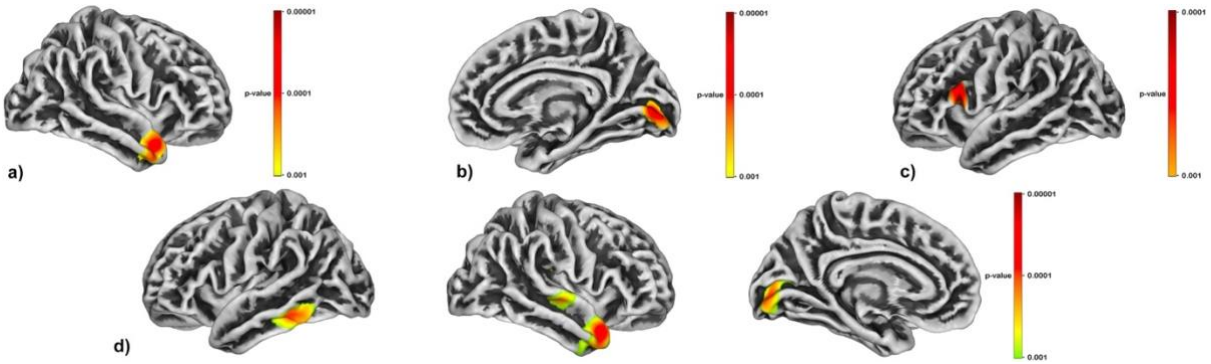

Figure 1*. Abnormal cortical complexity (CC) in Schizophrenia (SCZ) and Bipolar Disorder (BD). Patients with SCZ had (a) decreased fractal dimension (FD) in the right superior temporal gyrus when compared to healthy controls (HC). Patients with BD had (b) increased FD in the left lingual gyrus and (c) decreased FD in the left pars opercularis compared to HC. When comparing between diagnoses, FD was reduced in the left inferior temporal gyrus, the left lingual gyrus, the right temporal pole, inferior and superior temporal gyrus in SCZ relative to BD. Statistical maps are displayed at p < 0.001 uncorrected and p < 0.05 Family Wise Error (FWE) cluster-level corrected. The color bar represents the p-value.*

2.3.2 Correlation between imaging and clinical data

With regards to clinical symptoms, CC in the right superior temporal gyrus was associated with the hallucination domain of the SAPS scale in SCZ (r=0.353, p=0.027). In BD, CC in the left lingual gyrus was positively correlated with the mania domain of the BPRS (r=0.358, p=0.016 (Fig. 2).

Correlations with drug treatment. We did not find any significant correlation between FD values and psychotropic drug treatment in none of the patient samples: lithium and mood stabilizers (BP: ρ=-0.220, p=0.146; SCZ: ρ=0.124, p=0.452), antidepressant (BP: ρ=0.120, p=0.431;

SCZ: ρ=0.071, p=0.667), and antipsychotic medication (BP: ρ=0.041, p=0.790; SCZ: ρ=0.055, p=0.739).

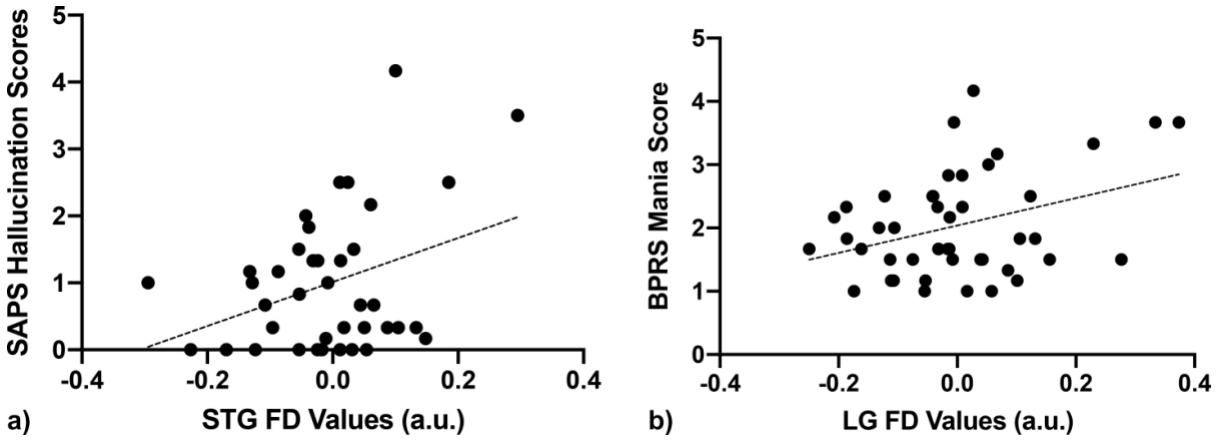

Figure 2. Correlation between imaging data and neuropsychological variables. a) In schizophrenic patients, the fractal dimension values in the superior temporal gyrus correlated with the hallucination domain of the SAPS scale (r=0.353, p=0.027). b) In bipolar patients, the fractal dimension values in the left lingual gyrus were correlated with the mania domain of the BPRS (r=0.358, p=0.016).

2.4 Discussion

FD was reduced in SCZ compared to HC in the right superior temporal gyrus (rSTG) and this is consistent with previous literature (Choi et al., 2020). Concerning clinical symptoms, FD in the rSTG was associated with the Scale for the Assessment of Positive Symptoms (SAPS) hallucination score in SCZ. The rSTG has a key role in auditory and language processing and previous studies support the association between neural alterations in rSTG and auditory verbal hallucinations (Palaniyappan & Liddle, 2014). BD displayed significantly lower CC in the left pars opercularis relative to HC. This finding is consistent with a mega-analysis that found reduced cortical thickness in this region and may be associated with its role in processing emotionally salient stimuli (Hibar et al., 2018). Additionally, BD had increased FD in the left lingual gyrus (lLG) and this measure was positively correlated with the Brief Psychiatric Rating Scale (BPRS) mania score.

Previous literature showed altered FD in several cortical regions in BD (Nenadic et al., 2017) and cortical thickness in the medial occipital cortex was correlated with mania severity (Kim et al., 2020). When compared to SCZ, BD showed a significant FD increase in the left inferior temporal gyrus, lLG, right temporal pole, inferior and superior temporal cortex. Altered neurodevelopment as reflected by neurological soft signs and cognitive impairments has been reported in SCZ as well as in BD (Valli et al., 2019). Notably, CC gradually develops in the pre/perinatal age, with small changes happening until the age of 20 years, after which this measure remains stable throughout adulthood, thus being a viable neurodevelopmental biomarker of the changes taking place mostly in the late foetal/early postnatal life (White et al., 2010). Altered CC in SCZ and BD may support the neurodevelopmental hypothesis of these disorders, whereby these mechanisms may be different in the disorders thus leading to different clinical courses (Valli et al., 2019). Indeed, a study investigating the effects of polygenic risk scores for psychiatric disorders on CC using found a marginal association with SCZ but not with BD (Schmitt et al., 2021). Thus, suggesting that CC alterations may be more pronounced in schizophrenia, heterogeneous across disorders, and partially influenced by environmental factors. The cross-sectional design limits our ability to make inferences or causation regarding the neurobiological features underlying SCZ-BD spectrum disorders. Although pharmacological treatments may affect brain structure (Centorrino et al., 2005), we did not find any effect of medications on CC. Future investigations and longitudinal research design that follow up patients during the course of the disorders will allow to progress our understanding of these findings.

Chapter 3

3. Study 2: The complexity of cortical folding is reduced in chronic cocaine users

The contents of this study have been accepted for publication in Addiction Biology.

3.1 Background

According to the 2021 report of the office of drug and crime of the United Nations, in the last year, around 275 million people have used drugs, about 5.4% of the global population aged 15/64 years, thus increasing by 22% from 2010 and forecasting a further increase by 11% by 2030 (United Nations : Office on Drugs and Crime, 2021). Only in the US over 70.000 drug overdoses occur annually, of which 21.2% are due to cocaine (Jovanovski et al., 2005). Cocaine-associated deaths also include long-term organic disability and neurocognitive deficits in attention, executive function, verbal memory, and response speed that could derive from sequelae of cardiovascular events due to the effects of this substance (Woicik et al., 2009). Moreover, co-occurrence of psychiatric conditions, including generalized anxiety disorder, depression, attention deficit hyperactivity disorder, or conduct disorder is commonly observed (Woicik et al., 2009).

Recent meta-analytic evidence has shown that patients with cocaine addiction (CA) present changes in the brain structure with significantly lower gray matter (GM) volumes in the right superior temporal gyrus, right insula, and right postcentral gyrus compared to healthy controls (HC), as well as increased GM volume in the right inferior parietal gyrus (Dang et al., 2022). In cocaine users, lower GM volume has been reported in the prefrontal and temporal cortex,

insula, striatum, and thalamus (Bittencourt et al., 2021). Interestingly, GM alterations seem to relate to the characteristics of substance use. Indeed, the duration of the drug intake is associated with abnormal GM volume in the right insula, right gyrus rectus, bilateral middle temporal gyrus, and right inferior frontal gyrus (Hall et al., 2015), while trait and behavioral impulsivity are related to the reduction of GM volume in fronto-parietal areas in cocaine users (Meade et al., 2020).

Although brain volume are related to surfaced-base measures, these latter indexes may be more sensitive to cortical reductions, as shown in several neuropsychiatry disorders and aging (Lemaitre et al., 2012). As expected, alterations in cortical measures have been shown in cocaine users. Particularly, in non-treatment-seeker cocaine users, Geng and colleagues observed a reduction in cortical thickness (CT) in the bilateral insula and an increase in the bilateral temporal lobe (Geng et al., 2017), that are crucial areas for the integration of visceral sensations, which can affect the decision-making process in addiction (Naqvi & Bechara, 2010). In addition, decreased CT in the superior frontal gyrus, inferior frontal gyrus, and orbitofrontal cortex (OFC) was described in cocaine users as well as smaller cortical surface area (CSA) in the anterior cingulate cortex (Hirsiger et al., 2019). Conversely, a recent investigation exploring gyrification in the orbitofrontal cortex (OFC) in cocaine users reported no significant differences from the control group (Hirsiger et al., 2019).

Recently, novel measures have been introduced to describe the morphology of the cortical surface and to assess the cortical complexity in the fractal dimension. FD is a non-linear measure derived from fractal geometry that summarizes morphological aspects of an object, by providing a numerical value of self-similarity, as a way to outperform traditional Euclidian geometry for the description of complex structures (Meregalli et al., 2022). In this sense, FD can be defined as a complexity index that assesses how a detail in a fractal pattern varies across multiple measuring scales. Considering that the highly convoluted brain cortex represents a fractal structure, we can apply this very concept on the study of the grey matter (GM), as its complex cortical folding (CC) can be examined through fractal geometry tools (Meregalli et al., 2022). FD can be used to describe cortical complexity in clinical and healthy

populations, as it is sensitive to detect morphological changes related to pathological and developmental changes (Trevisan, Jaillard, et al., 2022). Compared to VBM, surface-based analysis seems to be less influenced by inaccuracies in anatomical normalization during preprocessing, likely contributing to the heterogeneity of volumetric results (Tucholka et al., 2012). CC can provide quantitative information on cortex convolution, gathering in a single numeric value cortical thickness, sulcal depth, and folding area (Free et al., 1996). CC is more temporally stable than volume-based measures of GM (Yotter et al., 2011a). This measure increases from fetal age to adulthood, until it starts a slow and stable decrease until later in life (Zhang et al., 2016). FD changes have been found in several neurological and psychiatric disorders, including multiple sclerosis, dementia, stroke, and schizophrenia (King et al., 2009), with most studies showing a reduction in FD, thus suggesting that this measure can reflect alterations of brain function, e.g., in multiple sclerosis, in which it predicts the worsening of disability (Roura et al., 2021). Interestingly, findings from human studies and animal models examined how impulsivity, a construct commonly defined as deficits in the inhibition of behaviors, is a risk factor for the emergence of substance use disorders (SUD) (de Wit, 2009). In general, deficits in impulse control have been consistently reported in subjects with SUD. Addiction is usually associated with an impairment in the ability to ignore drug-related stimuli, but attentional biases in SUD patients are also present in more general nonspecific reward-related situations (Anderson et al., 2013). Attentional biases could be one of the mechanisms by which impulsivity affects addictive behaviors. This may be caused by the biasing of classical conditioning processing and by affecting the dopaminergic system (Coskunpinar & Cyders, 2013). Several instruments have been developed to measure the distinct facets of impulsivity, including the Barratt Impulsivity Scale (BIS-11), which allows the evaluation of a specific Attentional Impulsiveness subdomain (Patton et al., 1995). Structural MRI studies have been carried out to determine the neural correlates of impulsivity, both in healthy controls and in a clinical population where impulsivity is an important factor, such as patients with ADHD and bipolar disorders. In the healthy population, the volume of the orbitofrontal cortex has a tendency to correlate negatively with the impulsivity measured by the BIS-scale (Matsuo et

al., 2009). Specifically, attentional impulsivity seems to correlate negatively with the temporal gyrus volume in healthy controls, while the orbitofrontal was associated negatively in psychiatric patients characterized by impulsive behaviors (Lee et al., 2011).

In this study, our objective was to investigate CC in patients with cocaine addiction using FD. Since the frontal, parietal, temporal and insular cortices have been shown to play an important role in decision making and impulsivity (Meade et al., 2020), we hypothesised that CC in the brain of patients with cocaine addiction would be altered in these regions. Moreover, impulsivity is commonly associated with cocaine and the development to its addiction, with cocaine addicts usually showing higher scores on the BIS-11 scale when compared to healthy controls (Kaag et al., 2014). In particular, high impulsivity also predicts the shift from impulsivity to compulsivity during the development of addictive behaviors (Belin et al., 2008). In agreement with this, neuroimaging studies have shown a relationship between impulsivity and cortical volume and surface area of the frontal, temporal, and insular cortex (Kaag et al., 2014). We suppose that CC, being less influenced by preprocessing biases (Tucholka et al., 2012) and representing by itself a series of VBM values (Free et al., 1996), can resume alterations that other analysis could not. As a promising index of brain alteration(King et al., 2009) more temporally stable than volume-based measures of GM(Yotter et al., 2011b), CC could be less susceptible by aging bias and considered a pure value of neuronal damage. Moreover, CC summarizes linked elements of the gray matter in a single measure, including cortical thickness, sulcal depth, and surface area, and results in a greater precision to detect brain changes relative to each individual index (Meregalli et al., 2022). Finally, we predicted the association between CC changes and 1) the duration of cocaine use for its widespread neurotoxic effects and 2) impulsivity characteristics (in particular, for the attentive subdomain) in those regions implicated in the predisposition to addiction. To reduce the heterogeneity of neural effects due to sex differences (Andersen et al., 2012), we limited our investigation to men.

3.2 Materials and methods

3.2.1 Participants

CA and HC were selected from the Mexican database on cocaine use disorder (Angeles-Valdez et al., 2022). This open database contains demographic, clinical, and imaging data from 145 subjects who were recruited as part of a project on the study of addictions. Cocaine addiction was assessed using the MINI Mini-PLUS interview in Spanish version 5.0.0, which uses the DSM-IV criteria. Additionally, the instant view drug screening test was applied to screen for illicit substances other than cocaine (amphetamines, methamphetamines, benzodiazepines, cannabis, and opioids), thus excluding participants who showed a current dependence (based on the DSM-IV criteria) of substances other than cocaine and nicotine. Moreover, lifetime use of other drugs was evaluated using the Addiction Severity Index. Due to the low number of female participants in the study and to reduce sex-dependent heterogeneity (Andersen et al., 2012), we selected only male participants. Furthermore, we excluded patients with psychiatric or neurological comorbidities. To evaluate the association between FD and cocaine use characteristics, we excluded participants from the CA group whom daily cocaine intake was not specified in the database. The final sample included 52 CA and 36 HC. Demographic data, history, and current substance use were collected (see Table 1 for sample details). Furthermore, participants with a history of schizophrenia, bipolar disorder, mania or hypomania, or with family history of any neurological disorder were excluded from the dataset.

Moreover, the Barratt Impulsivity Scale (BIS-11), which allows the measurement of impulsivity and its subdomains, including Attentional Impulsiveness, Motor Impulsiveness, and Non-planning Impulsiveness, was administered (Patton et al., 1995). All participants underwent detailed cognitive assessment of cognitive flexibility, inhibition, working memory, decision making, and executive functions using the following tests (Angeles-Valdez et al., 2022): Berg's card sorting test (BCST), Flanker task, Go/No-go task, Letter number sequencing, Digit span

backward, Iowa gambling task, Tower of London. Cognitive performance was compared between CA and HC using ANCOVAs with age and education as nuisance variable.

	Patients with cocaine addiction (N=52)	**Healthy controls (N=36)**	**χ^2 or t**	**p**
Age (M±SD, years)	31.3 ± 6.51	30.1 ± 7.62	0.795	0.429
Education (M±SD, years)	10.9 ± 2.9	13.2 ± 3.53	-3.276	0.002
Total intracranial volume (M±SD, µl)	1442.7 ± 104.6	1460.4 ± 98.31	-0.796	0.428
BIS Total score (M±SD)	61.1 ± 14.6	40.2 ± 10.4	6.52	<0.001
BIS Attentive score (M±SD)	17.1 ± 5.23	11.6 ± 5.23	4.79	<0.001
BIS Motor score (M±SD)	18.4 ± 7.79	13.3 ± 5.72	2.97	0.004
BIS NonPlanning score (M±SD)	25.6 ± 6.82	15.3 ± 5.29	6.70	<0.001
Duration of cocaine use (M±SD, years)	10.8 ± 6.4			
Age of onset of cocaine use (M±SD, years)	20.7 ± 4.99			
Mean dose of cocaine (grams) per week in the last year (dose=n)	0.33= 6 0.33-0.66= 11 1-4= 22 4-8= 5 8-10= 2 >10 = 3 n/a = 3			
Method of drug administration (n)	Smoking=35 Inhalation = 13 Both= 4			
Time since last use (M±SD, days)	11.6 ± 10.4			
Polysubstance abuse				
Tobacco (n)	43			
duration tobacco use (M±SD, years)	14.6 ± 8.06			
benzodiazepines (n)	2			
cannabis (n)	4			

Table 1. *Demographics, brain size, impulsivity in the study samples, and current and past substance abuse. BIS, Barratt Impulsiveness Scale; M, Mean; SD, Standard deviation*

3.2.2. Brain imaging

Brain images were acquired on a Philips Ingenia 3T MR system with a 32-channel head coil with the following parameters: The T1-weighted images were acquired using a three-dimensional FFE SENSE sequence, TR/TE = 7/3.5 ms, field of view = 240, matrix = 240 × 240 mm, 180 slices, gap = 0, plane = sagittal, voxel = 1 × 1 × 1 mm (five participants were acquired with a voxel size = 0.75 × 0.75 × 1 mm), scan time = 3.19 min.

Preprocessing. We used the Statistical Parametric Mapping analysis package (SPM12) together with the Computational Anatomy Toolbox for SPM (CAT12). For preprocessing and analysis, we applied default parameters in accordance with a standard protocol (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf).

In detail, T1 images were spatially registered to the Montreal Neurological Institute (MNI) template using DARTEL registration. Brain structural data were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) and then used for the reconstruction of the cortical surface for each participant using the projection-based thickness method (Dahnke et al., 2013). The total intracranial volume (TIV) was calculated as the sum of the volumes of GM, WM, and CSF. The central surface reconstruction included topology correction, spherical inflation, and registration. The central surface was used as input to calculate the fractal dimension values. Finally, all surface measures for both hemispheres were merged and resampled to a resolution of 32k mesh. We also included a two-step quality check: First, all images were visually inspected for artifacts before preprocessing. Then, after segmentation, the images underwent a statistical quality control for inter-subject homogeneity and image quality, as included in the CAT12 toolbox.

The CC was analyzed following the specifics implemented in CAT12, using the “spherical harmonic reconstruction” approach proposed by (Yotter et al., 2011a). To increase the signal-to-noise ratio, given the average distance between the sulci and the gyri, the resampled surface data for the CC values were smoothed using a 25mm (and repeated using a 20mm to

exclude a significant effect of the smoothing filter) Gaussian FWHM kernel before the second level analyses."

3.2.2 Statistical analysis

Demographic data were compared between the CA and HC groups using two-sample t-tests. Total and subdomain scores of BIS-11 were compared between the groups using an ANCOVA, with age and years of education (for BIS-11 scores) as covariates. A voxel-wise general linear model with age as a covariate was used to compare the CC between the two groups. Nonparametric permutation-based testing was applied to t-stat maps using the threshold-free cluster enhancement (TFCE) method with 10.000 permutations to correct for multiple comparisons with the family-wise error (FWE) approach at the cluster level with $\alpha = 0.05$. To exclude that drug administration methods could have affected our results, CA were stratified for this variable, and CC was compared using one way ANOVA. Furthermore, to rule out a possible confounding effect of education differences between groups, CC differences between CA and HC, ANCOVAs were performed on the CC values of the clusters showing a significant effect of diagnosis with years of education as a nuisance covariate. To investigate the correlation between clinical and imaging data in patients, we used a partial Pearson's correlation between the addiction duration indexes (duration/age of onset), weekly dose (average weekly dose in grams of cocaine in the last year), BIS total and subscale scores, and CC in those clusters showing an effect of diagnosis. Furthermore, to investigate the correlation between clinical, cognitive and imaging data in patients, we used a partial Pearson's correlation between addiction duration indexes (duration/age of onset), weekly dose (average weekly dose in grams of cocaine in the last year), BIS total and subscale scores, cognitive performance on each neuropsychological test and CC in those clusters showing an effect of diagnosis using education as covariate.

3.3 Results

3.3.1 Demographical and Clinical Data

The groups did not differ with respect to age (CA, 31.28±6.51 years; HC, 30.08±7.62; p= 0.428 years) and showed a significant difference in education (CA 10.94±2.90 years, HC 13.19±3.52 years, p= 0.001). The mean age of onset of cocaine addiction was 20.65±4.99 years. The drug administration methods were smoking only (n=35), inhaling only (n=13), and both (n=4). Current polysubstance use included cannabis (n=4) and benzodiazepines (n=2). None of the patients was using opioids or amphetamines at the time of evaluation (Table 1). CA patients had a higher BIS-11 total ($p<0.001$) and all subdomain scores: Attentional ($p<0.001$), Motor ($p=0.004$), and Non-Planning ($p<0.001$) when compared to HC (Table 1). Regarding cognitive performances, CA showed poorer performance compared to HC at the BCST in the following indexes: categories concluded ($p < 0.001$, $t = -4.14$) categories experienced ($p < 0.001$, $t=-4.14$); correct responses ($p = 0.008$, $t=-3.37$); total mistakes ($p = 0.008$, $t=3.41$). All other cognitive assessments did not show any significant differences between the diagnostic groups.

3.3.2 Cortical Complexity

CA showed reduced CC compared to HC in a cluster that included the left insula and the left part of the supramarginal gyrus (SMG, cluster peak at x, y, z= -37, 7, -10; k= 1162, p= 0.008) (Figure 1.a) and in the left medial orbitofrontal cortex (cluster peak at x, y, z= -27, 48, 8; k= 307, p= 0.039) (Figure 1.b). There were no significant differences in CC within the CA group between the type of drug administration in the left insula and left SMG cluster [$F(df=2, 49)=0.243$, $p=0.784$)] and the left medial orbitofrontal cortex cluster [$F(df=2,49)=0.477$, $p=0.623$)]. These results did not change when 20 mm Gaussian FWHM kernel smoothing was applied.

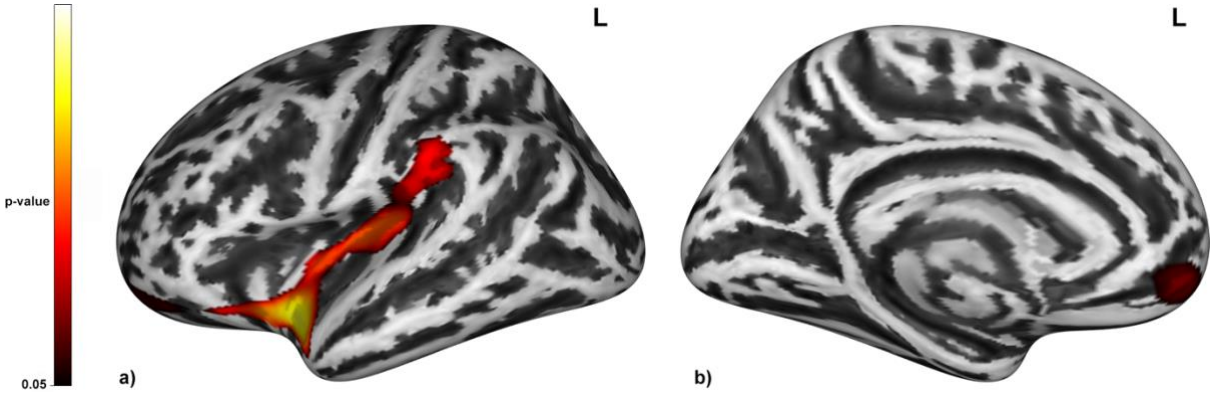

Figure 1. *Increased complexity of cortical folding (CC) in patients with cocaine addiction (CA) in the left (a) lateral and (b) medial hemispheres. CC was reduced in patients with CA in a cluster that spans the left insula and the left part of the supramarginal gyrus (a) and in the left medial orbitofrontal cortex (b) compared to healthy controls (HC). Statistical maps are displayed at p<0.001 uncorrected and p<0.05 family-wise-error (FWE) cluster-level corrected. The color bar represents the p-value.*

3.3.3 Correlations with cocaine use characteristics, impulsivity scores and cognitive perfomances

The CC values in the medial OFC were positively correlated with the age of onset of cocaine addiction (r= 0.310, p= 0.028) (Figure 2.a). In addition, in the CA group, the CC values in the medial OFC were positively correlated with the attentional subdomain of the BIS score (r= -0.307, p= 0.048) (Figure 2.b). No other correlations were found between the CC values and cocaine dose or impulsivity scores. Finally, We did not find any significant correlation with cognitive performance.

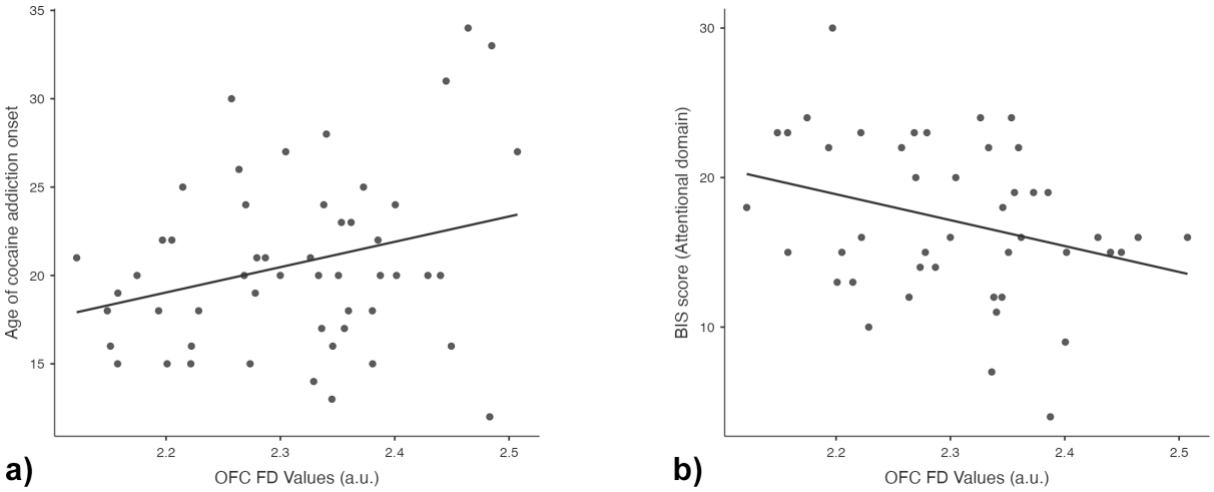

Figure 2. *Scatter plot of the complexity of cortical folding (CC) and the age of onset of cocaine addiction (a) and the attentional subdomain of the Barratt Impulsiveness Scale (BIS) (b). The CC in the left medial orbitofrontal cortex (OFC) was positively correlated with the age of onset of cocaine addiction (a). The CC in the left medial orbitofrontal cortex (OFC) was negatively correlated with the attentional subdomain of the BIS (b). Age is measured in years, CC in arbitrary units (a.u.), and BIS score is an absolute value. The line represents the best fit.*

3.4 Discussion

To our knowledge, this is the first study to investigate changes in the complexity of cortical in patients with chronic cocaine addiction. Our main finding is that patients with chronic cocaine addiction, compared to controls, showed a lower CC in the left insula, supramarginal gyrus, and medial orbitofrontal cortex. The CC in the left medial orbitofrontal cortex was positively correlated with the age of onset of cocaine addiction and negatively with the total years of cocaine addiction. Furthermore, CC in the left medial orbitofrontal cortex of cocaine users was negatively correlated with the attentional subdomain score of the BIS scale.

A wide body of research has shown that drug-taking behaviors that occur after exposure to substances can be related to altered neural circuits involved in motivation, decision-making, and learned associations (Volkow & Fowler, 2000). More specifically, the prefrontal cortex (PFC), and in particular the OFC, appears to be a key player in the development of addictions, due to its role in decision-making, reward-based, and goal directed-behavior (Volkow & Li, 2004). The PFC is essential for cognitive processes such as attention, working memory,

decision making, cognitive control and delay discounting, all of which are compromised in addicted individuals (George et al., 2008). Clinical studies have reported a pattern of generalized PFC dysfunction in drug-addicted individuals, which seems to be associated with worse outcomes (e.g., greater drug use, poor performance of PFC-related tasks, and higher likelihood of relapse) (George et al., 2008). Additionally, structural imaging studies have shown a reduction in PFC thickness in individuals with SUD, not only for cocaine addiction but also for other substances (Chumachenko et al., 2015). Within the PFC, GM loss is more evident in dorsolateral PFC, ACC, and OFC, and is correlated with longer duration and greater severity of drug use (Chumachenko et al., 2015). Cortical thinning in the OFC and in the insula has been previously reported in patients with cocaine addiction and is associated with long-lasting changes in the OFC that impair voluntary control. This may be due to a general decrease in baseline metabolic activity in this region and a reduction of dopamine D2 signals (Volkow & Li, 2004). Additionally, disruption of the OFC has been linked to compulsive behavior and disinhibition (Woicik et al., 2009). We found a decrease in CC in the left mOFC in CA. Decline in CC has been associated with altered brain structure in neurodegenerative disorders characterized by cognitive impairment, including Alzheimer's disease, frontotemporal dementia, and mild cognitive impairment (Nicastro et al., 2020). Reduced CC can be associated with impaired cognitive performance, and may underlie reduced response inhibition ability that is associated with impulsivity (vide infra). In particular, we found a correlation between CC in the left mOFC and the age of onset of cocaine use, suggesting a dose-effect relationship between cocaine use and the organization of the brain structure. Notably, this result is in line with a recent longitudinal investigation showing that changes in cortical thickness in the frontal cortex in cocaine users were linked to the amount of cocaine consumed over the study period (Hirsiger et al., 2019).

Furthermore, CC in the cluster of reduced OFC was negatively correlated with the attentional domain of the BIS. Consistent with the literature on cocaine use, patients with CA had greater impulsivity that affected all subdomains in our study (Winhusen et al., 2013). Furthermore, CA is characterized by impairments in attentional skills and a significant attentional bias towards

cocaine-related stimuli (Hulka et al., 2015). In general, patients with SUD have an overall impairment with the processing of reward-related stimuli, due to cognitive and attentional biases (Anderson et al., 2013). Our results suggest that impaired impulsivity, and ultimately cognitive biases in SUD, may be linked to the reduced CC of the OFC (Anderson et al., 2013) (Figure 3).

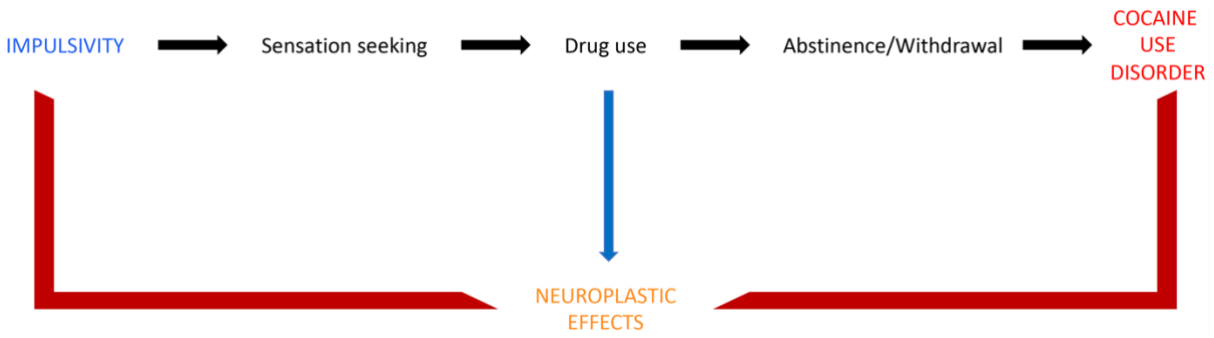

Figure 3. *Relationship between brain changes, impulsivity, and cocaine use disorder.*

Similar findings of a correlation between GM volume and addictive behavior have been described in animal models. Alterations in cortical and sub-cortical GM volume have been correlated with behavioral sub-dimensions of addiction, such as high motivation for drug taking (mPFC), maintenance of drug use despite negative consequences (SC and PAG), and persistence of drug seeking (motor, somatosensory, association, insular cortices, and amygdala) (Cannella et al., 2018). Animal studies investigating the impact of chronic use of cocaine on drug-related behavior and brain structure in rats have found that cocaine exposure can induce persistent structural alterations in the regions implicated in addiction, such as nucleus accumbens, ventral pallidum, striatum, substantia nigra, insular cortex and OFC (Otaka et al., 2013). Furthermore, these changes appear to be most pronounced when drug exposition occurs early during adolescence. These findings suggest that cocaine use could induce brain changes that contribute to the reinforcement of addicted behavior (Wheeler et al., 2013). The impairment of set-shifting abilities in our study supports this idea (Madoz-Gúrpide et al., 2011).

We also found a reduction in CC in the left insula in CA. Insula is involved in the integration of visceral sensations, which may affect the decision-making process in addiction (Naqvi & Bechara, 2010). This region sends input to the OFC, where they can inform decisions and guide actions (Penfield & Faulk, 1955). In particular, the connections between the insula and the ventro-tegmental area and the substantia nigra can play a crucial role in the development of addictions with modulation of dopamine signaling (Penfield & Faulk, 1955). Animal models investigating the learning processes underlying the association of external signals with the rewarding effects of drugs have shown that the insula is involved in the perception of bodily needs guiding motivated behaviors, with a key role for the interoceptive insular cortex in the craving for the drug in animals exposed to amphetamine (Koob & Volkow, 2016). Recent investigations have found significant alterations in the insular cortex in patients with different types of addiction (Battistella et al., 2014), including cannabis, online gaming addiction, social media, and smoke. In particular, a reduction in GM volume and cortical thinning in the insula were demonstrated in both cocaine and heroin-dependent patients (Bittencourt et al., 2021). Structural alterations in the insula may affect the interaction between cognitive and affective processes in decision making and ultimately contribute to the lack of avoidance responses to aversive events that can underlie drug-seeking behavior and craving.

We found reduced CC in SMG. Recent studies have indeed shown that a reduction in GM volume in SMG predicts craving symptoms in cocaine addiction (Barrós-Loscertales et al., 2011). Reduced connectivity between SMG and the ventral striatum, a brain circuit involved in emotional perception and awareness that has been associated with stimulant addiction (Ersche et al., 2020). Thus, the role of altered cortical complexity of SMG may be associated with an altered ability to control impulsive responses, including craving, motivational effects and maintenance of addicted behavior through cognitive control deficits such as dysregulation of incentive salience assigned to drug-related stimuli (Costumero et al., 2018).

Overall, our study provides evidence that cocaine abuse alters the complexity of cortical folding in specific brain regions involved in enteroception, decision-making, and response inhibition. With our cross-sectional design, we cannot determine whether our findings

predispose to or result from addiction. However, the relationship between the altered CC in OFC and the duration of cocaine abuse suggests that this alteration may follow local neurotoxic or ischemic effects (Glauser & Queen, 2007). This observation is in line with evidence from animal studies that shows that repeated exposure to cocaine can induce long-lasting changes in brain morphology, including inhibition of neurite extension, reduction in dilation of the endoplasmatic reticulum, abnormal lysosomal proteolysis and disturbed neuronal mitochondrial dynamics (Wen et al., 2022). Notably, these cellular and molecular adaptations induced by cocaine appear to be linked to epigenetic changes, defined as regulations of gene expression, independently of the DNA sequence, that result from the interactions between environmental factors and the individual's genome (Pierce et al., 2018). In cocaine addiction, numerous studies have reported cocaine-induced changes in epigenetic mechanisms, including histone modifications, DNA methylation, and microRNAs (Hirjak et al., 2017).

At the same time, although impulsivity is considered both a determinant and a consequence of drug use, including cocaine use, our findings of a relationship between the reduced complexity of cortical folding in this region and attentional impulsivity argues in favor of a preexisting condition that can underlie the risk of the disorder. Cocaine addiction is a complex disorder with genetic and environmental factors playing an important role individually and in interaction (Glauser & Queen, 2007), and the neurobiology revealed from CC seems to support this idea.

On the other hand, Previous studies have investigated the relationship between cortical thickness, gyrification, cortical surface area, and CC (which are thought to have distinct neurodevelopmental trajectories) and impulsivity traits in healthy young adults (Hirjak et al., 2017). Overall impulsivity was associated with higher local gyrification index (LGI) (particularly in temporo-parietal regions), with separate regions predicting distinct types of impulsivity: fronto-temporo-parietal regions for nonplanning impulsivity, and fronto-parietal and occipital areas for attentional impulsivity, respectively (Hirjak et al., 2017). The authors suggested that

variations in LGI (a marker of early neurodevelopment that was altered in the fronto-temporo-parietal cortex) could lead to increased impulsivity in healthy individuals. Furthermore, cortical thickness (but not surface area) in the temporal, superior parietal, and occipital cortex was negatively associated with higher global impulsivity in healthy individuals (Kubera et al., 2018). Taken together, these findings suggest that alterations in brain structure and in cortical folding may reflect abnormalities in neurodevelopment and correlate with impulsivity traits also in healthy subjects without exposure to substances, thus representing a possible signature of vulnerability to addiction behaviors, that predates the neuroplastic effects of substances.

Overall, the relationship between cocaine abuse and cortical alterations is complex and not yet fully clarified. Not only can CC alterations in CC can be a sign of a vulnerability trait leading to CUD (through impulsivity traits) but the substance itself can also cause changes in the cerebral cortex. Although genetic factors can directly contribute to cocaine dependence (heritability = 0.4-.7) (Fernàndez-Castillo et al., 2022) cocaine itself can affect gene expression in the prefrontal cortex and the midbrain, thus leading to functional and structural changes in the brain, including synaptic plasticity and neural connectivity, that are partly stable and can contribute to addiction and relapse in CUD (Fernàndez-Castillo et al., 2022). Animal studies show that prolonged exposure to cocaine can lead to impaired attention, and this bias is selectively mediated by altered OFC activity (Baeg et al., 2020).

We must acknowledge some limitations of this study. First, the sample consisted of only men, which limits the generalizability of the results to women. However, addiction in general and to cocaine presents several differences between the sexes, including the severity of craving, medical and psychiatric comorbidity, and social, family, and employment problems (Andersen et al., 2012). Therefore, including only men should have reduced the heterogeneity of our results. Second, our study is cross-sectional and therefore cannot determine the causal relationship between brain changes and substance use disorder. Despite these limitations, to our knowledge, this is the first study to investigate the complexity of cortical folding in patients with cocaine addiction.

In conclusion, we show that the cortical surface morphometry, measured by the complexity of the cortical folding, is altered in cocaine addiction. Our results support the idea that the development of cocaine addiction may be associated with neurobiological alterations that underlie the vulnerability to this disorder. In its turn, the use of cocaine can affect the neural circuits that mediate behavior that support the addiction process itself with a feedforward mechanism. These theories are also supported by previous findings of cortical alterations in individuals with other substance use disorders (i.e., cannabis, alcohol, hallucinogens, stimulants) and addictive behaviors (i.e., online gaming), suggesting that cortical abnormalities might be implicated in the pathophysiology of addictions. Moreover, recent evidence has shown that cortical alterations are associated with impulsivity in neurodegenerative disorders(Meregalli et al., 2022), supporting the theory that structural cortical abnormalities might contribute to higher impulsivity, which in turn represents a risk factor for substance use disorders. Future longitudinal studies with a larger sample size including subjects with other substance or behavioral addictions are warranted to unravel the contribution of these processes in the development of addictions.

Chapter 4

4. Study 3: Surface-Based Cortical Measures in Multimodal Association Brain Regions Predict Chess Expertise

The contents of this study have been published in Brain Sciences (Trevisan, Jaillard, et al., 2022):

Trevisan N, Jaillard A, Cattarinussi G, De Roni P, Sambataro F. Surface-Based Cortical Measures in Multimodal Association Brain Regions Predict Chess Expertise. Brain Sci. 2022 Nov 21;12(11):1592. doi: 10.3390/brainsci12111592.

4.1 Background

The game of chess is a complex intellectual activity that provides a useful model for the study of memory, attention, perception, visuospatial cognition, and problem-solving (Charness, 1992). Success in chess appears to be related to several factors, including experience in chess playing, participation in tournaments, fluid intelligence, spatial processing, and social cognition(Atherton et al., 2003). A good performance in chess is related to intensive practice over the years, with a minimum of ten years of practice required at the grandmaster level (Simon & Chase, 1988). Cognitive factors may also contribute to chess expertise. A meta-analysis of cognitive abilities in chess players showed that chess skills are positively correlated with fluid intelligence, comprehension, general knowledge, working memory, and processing speed (Burgoyne et al., 2016).

Morphological neuroimaging studies explored how structural measures contribute to determining the neural correlates of chess expertise. Voxel-based morphometry (VBM) studies reported structural differences by comparing brain cortical and subcortical structures

between chess players and novices with little or no experience in the chess game. Overall, chess players show decreased gray matter (GM) volume and cortical thickness (CT) in the caudate nucleus (Duan et al., 2012), the frontal and parietal gyri (Ouellette et al., 2020), and the occipitotemporal junction, along with increased mean diffusivity in the left superior longitudinal fasciculus (SLF) (Hänggi et al., 2014). A recent study reports thinner CT in expert chess players compared to novices in the bilateral frontoparietal regions (Ouellette et al., 2020). Moreover, greater expertise is correlated with decreased mean diffusivity in the right SLF (Hänggi et al., 2014), and the duration of professional training and cognitive scores are associated with diffusion measures in the association white matter tracts, including the uncinate fasciculus, inferior longitudinal (ILF), and SLF (Mayeli et al., 2018). Taken together, these studies suggest that chess expertise is associated with structural changes in a distributed network of regions engaged in cognitive tasks related to intelligence and visuospatial abilities with rather low regional specificity.

Brain volumetric approaches (e.g., VBM) are robust methods that have been extensively used for the study of neurophysiological processes, as well as for neuropsychiatric disorders. Unfortunately, these methods may be inaccurate during spatial normalization to a standard template (Ghosh et al., 2010) for registration errors and may produce inflated statistics (Scarpazza et al., 2015) (see Goto et al. (Goto et al., 2022), for a more detailed comparison of the two approaches). Complementary to this approach, surface-based morphometry was introduced to provide more accurate information on cortical changes relative to VBM (Ghosh et al., 2010). Indeed, surface-based morphometry can measure different properties of the cortical surface, including the gyrification index (GI) and the fractal dimension (FD). In particular, GI is defined as the ratio of the pial surface area to the surface area of the cortical hull or the outer contour of the brain (Gregory et al., 2016). GI in a large set of associated regions is associated with general cognitive ability and intelligence, accounting for 5–12% of the variance in general intelligence (Tadayon et al., 2020). FD is a nonlinear measure derived from fractal geometry that quantifies self-similarity, a measure that outperforms traditional Euclidean geometrics for the description of irregular surfaces. FD can be defined as an index

of complexity that assesses how a detail in a fractal pattern changes with a varying measuring scale. Since the highly convoluted brain cortex represents a fractal structure (Hofman, M. A, n.d.), FD has been used to describe the morphology of the brain cortical surface and to assess the cortical complexity at the level of the brain hemispheres, regions, and neurons (Yotter et al., 2011a).

Neuroimaging studies show that FD correlates with both morphological complexity and neuronal maturity (T. Liu et al., 2011). Furthermore, recent work in the literature shows that FD is associated with fluid intelligence, particularly information processing, and the ability to generate, test, and refute multiple hypotheses simultaneously (Franconeri et al., 2013). Therefore, FD appears to be closely related to working memory, attention, and visuospatial processing (Tadayon et al., 2020), which are crucial skills in the expertise of chess.

Gyrification is considered a potential marker of early neurodevelopment since the formation of gyri and sulci in the brain begins between 10 and 15 weeks of human fetal life and reaches its peak during the third trimester of fetal life (White et al., 2010). Conversely, FD increases from fetal life through childhood and into adulthood, until it starts to decrease later in life (Shyu et al., 2010). Interestingly, both GI and FD provide useful information on cognitive abilities due to their close relationship with innate intelligence and with developmental changes, respectively (Tadayon et al., 2020). Furthermore, decreased FD has also been observed in several neuropsychiatric conditions associated with altered cognitive function (Meregalli et al., 2022).

In this study, our objective was to investigate changes in the brain surface of chess experts using GI and FD. We hypothesized that the surface indexes of the brain regions and networks underlying high-order cognition, including fluid intelligence, working memory, processing speed, and visuospatial processing, namely, prefronto-parieto-temporal networks, would be altered. Furthermore, since chess training usually starts during childhood, we hypothesized that these indexes would be correlated with the age of chess practice.

4.2 Materials and methods

4.2.1 Participants

We used data extracted from the Huaxi MR Research Center database [32]. This database contains healthy participants' data from 29 professional chess players (age: 28.72 ± 10.84 years; 9 females) and 29 novices (age: 25.76 ± 6.95 years; 15 females) with very limited skills and knowledge of the chess game. Professional chess players received rigorous training (training time: 4.24 ± 1.73 hours/day). They started playing at 8.50 ± 2.80 years old and professional training at 17.00 ± 5.80 years old, respectively. The professional chess players had an average score of 2401.1 ± 134.6 Elo chess skills. Specifically, 6 of them were rated grandmasters and 11 masters. Additionally, 23 of these professional chess players scored above the entry level for chess mastery by the standards of the United States Chess Federation. The two groups were matched for age, sex, and education (Table 1). All participants were right-handed and had no history of physical or mental disorders.

	Professional Chess Players (N = 29)	**Novices (N = 29)**	***p*-Values**
Age: mean (SD)	28.72 (10.84)	25.76 (6.95)	0.22
Sex: females (%)	9 (31.03%)	15 (51.72%)	0.11
Education: years (SD)	13.27 (2.79)	13.92 (3.15)	0.41
Elo rank: mean (SD)	2401.1 (134.6)	-	-
Age at which they started professional training: mean years (SD)	17 (5.8)	-	-
Duration of daily training: mean hours (SD)	4.12 (1.79)	-	-

Table 1. *Demographic and chess training characteristics of professional chess players (N = 29) and novice participants (N = 29).*

4.2.2 Brain imaging

Preprocessing. A high-resolution T1-weighted structural image was acquired for each subject, using an MPRAGE sequence. The scanning parameters were the following: TR = 1900 ms, TE = 2.26 ms, TI = 900 ms, bandwidth = 200 Hz/Px, FOV = 256 × 256 mm^2, flip angle = 9°, 176 slices, voxel size = 1 × 1 × 1 mm^3.

T1 images (Figure 1a) were spatially registered to the Montreal Neurological Institute (MNI) template, and then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) components (Figure 1b) using DARTEL (Ashburner, 2007). Segmented data were used to reconstruct the cortical surface of each participant (Figure 1c). The central surface reconstruction included topology correction, spherical inflation, and spherical registration. The central surface was used as an input to calculate GI and FD (Figure 1d). These values were analyzed following the specifics reported by (Dahnke et al., 2013), using the approach of "spherical harmonic reconstructions" proposed by (Yotter et al., 2011a). Finally, the mean values of FD, GI, and CT were extracted for 180 regions of interest (ROI) for each hemisphere (Figure 1e) as defined in the Human Connectome Project (HCP) multi-modal parcellation atlas (Glasser et al., 2016). All analyses were performed using the Computational Anatomy Toolbox for SPM (CAT12, http:// www.neuro.uni-jena.de/cat/ 16/12/2020).

To confirm our approach, we wanted to replicate the findings of Ouellette and colleagues on GI differences in professional chess masters in the same dataset using a different software (CAT12 vs. Freesurfer) and analysis approach (high-resolution ROI vs. whole brain) (Ouellette et al., 2020).

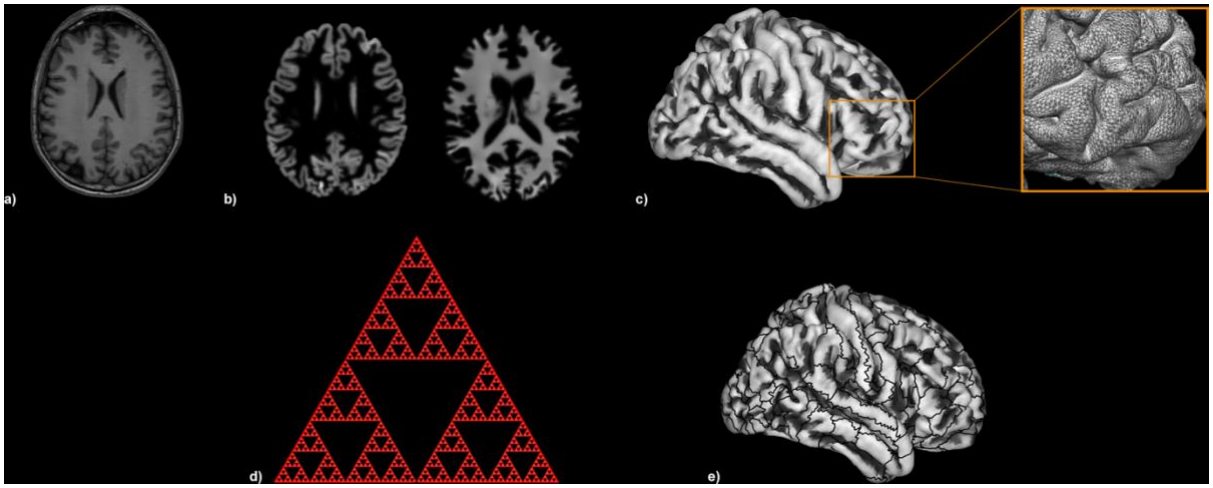

Figure 1. *Surface-based cortical measures [fractal dimension (FD) and gyrification index (GI)] estimation process. (**a**) Structural T1 image (in coronal orientation) was registered, normalized, and segmented to extract the; (**b**) grey matter (left) and white matter (right) components. From these maps (**c**) the cortical mesh was reconstructed using the projection-based thickness method (the inset illustrates an example of cortical mesh in the right prefrontal cortex); (**d**) the FD (in the figure, a Sierpiński triangle, which exemplifies the self-similarity concept, i.e., the large equilateral triangle can be decomposed into smaller equilateral triangles at different scales, is depicted) and the GI (not represented) were calculated from the cortical mesh; (**e**) the cortical surface was parcellated in 180 regions of interest (ROI) per hemisphere using the Human Connectome Project multi-modal parcellation atlas and FD and GI values were averaged within each ROI.*

4.2.3 Statistical analysis

Bivariate Analysis. Demographic data were tested for normality using the Shapiro-Wilk test. Bivariate comparisons were performed using chi-square tests for categorical variables and with two-sample t-tests or Mann–Whitney tests for continuous variables according to their distribution, with a false discovery rate (FDR) correction for multiple comparisons, respectively. The bivariate correlations between GI and FD and the behavioral variables provided in the dataset were carried out using Pearson's or Spearman's correlation tests according to the distribution of the variables. The correlations of variables related to the starting age of the chess training of the expert players were controlled by the age, sex, and education of the participants. The level of significance was set to $p < 0.05$ for all tests. We also performed an outlier analysis on the GI and FD values using the Grubbs' method and found no outliers in the data. Additionally, we performed vertex-wise whole brain two-sample t-tests between the two player groups, where the FD, GI, and CT measures for both hemispheres

were merged and resampled to a 32k mesh resolution, with a 25 mm smoothing with a full width half maximum Gaussian kernel (FWHM). We then used threshold-free cluster enhancement (http://www.neuro.uni-jena.de/tfce 16/12/2020) with 5000 permutations and applied a family-wise-error (FWE) corrected threshold of $p < 0.05$ to control for multiple comparisons.

Multivariate Analysis. To estimate the association of regional surface-based values with chess expertise, we performed logistic regression (LR) analyses, controlling for the effects of age, sex, and education. Two LR models (one for FD and another for GI) were estimated with chess skills as a dependent variable. Covariates were introduced in the model using block entry for demographic variables and a forward conditional stepwise method for regional GI and FD. The regions were pre-selected based on regions that reached significance in bivariate analyses comparing GI and FD in professional chess experts and novices at a threshold of $p < 0.05$ uncorrected. We evaluated the performance of the LR model using the chi-square likelihood ratio test, statistical tests of individual predictors (betas) using the Wald chi-square statistic and $p < 0.05$, goodness-of-fit using the Hosmer and Lemeshow test, and the Nagelkerke pseudo-R^2 index, and predicted probabilities using a classification table assessing model accuracy. Internal validation was applied to correct for overfitting with bootstrap based on 5000 replications. Finally, we determined the regions in which FD and GI were associated with chess expertise by assessing the sensitivity and specificity of the LR models using the receiver operator characteristic (ROC) providing an area under the curve (AUC) estimate, with the highest AUC considered as indicating the best model (see Supplementary Materials). Statistical analyses were performed using Jamovi software (Version 1.2, https://www.jamovi.org), RStudio (http://www.rstudio.com/), and SPSS (IBM SPSS Statistics for Windows, Version 20.0, IBM, Armonk, NY, USA).

4.3 Results

4.3.1 Cortical Complexity

Bivariate Comparison. Compared to novices, professional chess players show significantly higher FD values in the left frontal operculum OP5 (lFOP5, p = 0.030) and the precentral operculum (PrCO), and significantly lower FD values in the right area 7M (7 m, p = 0.030), after FDR correction for multiple comparisons.

From the additional whole-brain vertex-wise analysis, professional chess players show a cluster of significantly higher FD in an area located in the left frontal operculum (x, y, z = −34, 28, 13, k = 12, p = 0.010, FWE-corrected) (Figure 2).

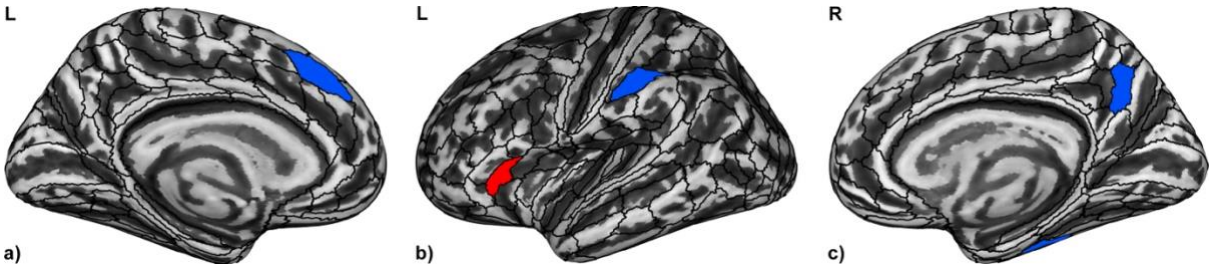

FIGURE 2. *Increased (in red) cortical complexity in the (**b**) left frontal operculum OP5 (left FOP5) and a decrease (in blue) in (**a**) the left caudal part of the dorsomedial prefrontal cortex (8BM), (**b**) the left inferior parietal lobule with a thin cortical ribbon (PFt) and (**c**) the right 7 m and right temporal area F (TF), respectively, predict chess expertise using logistic regression. L, left; R, right.*

4.3.2 Correlations with Chess-Related Features in Chess Masters

Increased FD in lFOP5 is inversely correlated with the starting age of professional chess training (ρ = −0.544, p = 0.007) (Figure 3a). Furthermore, reduced FD on the right 7 m of professional chess players shows a trend for negative correlation with the daily duration of chess training (ρ = −0.384, p = 0.040) (Figure 3b). No significant correlation is found between the FD and Elo scores.

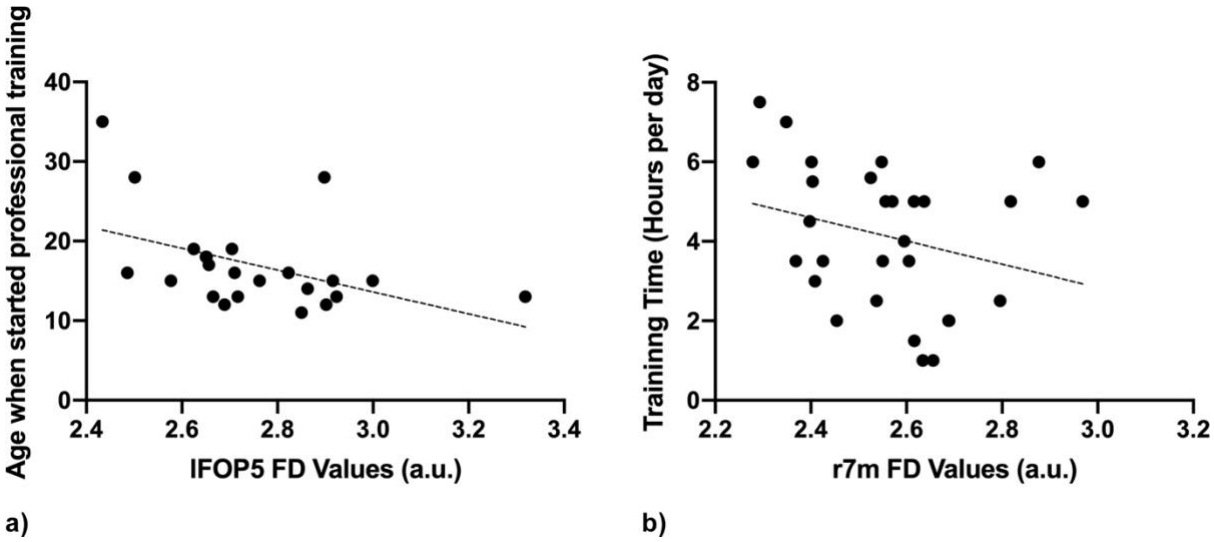

Figure 3*. Scatter plots of fractal dimension (FD) values and demographic and behavioral data among professional chess players. (a) The FD in the left frontal operculum OP5 (lFOP5) is correlated with the age (years) at which the participants begin their professional training (ρ = −0.503, p = 0.008). (b) The FD in the right area 7M (r7m) is correlated with the daily time spent in chess training (ρ = −0.403, p = 0.034). a.u. = arbitrary units.*

4.3.3 Regions Associated with Chess Expertise

The LR model controlling for age, sex, and education (Table 2) shows that chess expertise is predicted by increasing FD in the left FOP5 and decreasing FD in the right 7 m, right temporal area F (TF), left caudal part of the dorsomedial prefrontal cortex (8BM), and part of the inferior parietal lobule with a thin cortical ribbon (PFt). Chess expertise is associated with FD values in a set of association regions including the left fronto-opercular cortex, the right SPL/posterior cingulum and the lateral temporal cortex, and the fronto-medial and IPL cortices (Figure 2). Moreover, younger age is significantly associated with chess expertise, with no significant effect of sex or education. The efficiency of the model reaches 93.1%, the Nagelkerke R2 = 0.793, and the AUC = 0.961 (SE = 0.025, 95%CI = 0.912 to 1.000), indicating high model performance.

Predictors with Bootstrap						
	B	**Bias**	**SE**	**p**	**95% CI**	
					Lower	**Upper**
Age (years)	−0.10	−5.98	34.31	0.025	−52.27	1.27
Sex (male)	1.01	61.15	561.57	0.317	−135.33	595.34
Education	−0.24	−13.81	107.35	0.100	−118.85	16.58
ROIs						
Left FOP5	11.07	485.79	2869.57	0.001	5.94	3844.66
Left PFt	−7.25	−412.05	2380.84	0.000	−3538.41	−4.18
Left 8BM	−16.41	−698.42	3863.81	0.001	−5819.85	−9.42
Right TF	−8.92	−404.94	2514.75	0.004	−3164.28	−3.45
Right 7 m	−7.67	−214.67	1686.45	0.002	−1616.48	63.18
Intercept	74.24	3258.26	18,208.48	0.000	51.04	26,353.63

Classification table			
	Predicted		
Observed	Novices	Professional chess players	Correct %
Novices	26	3	89.7%
Professional chess masters	1	28	96.6%
Overall percentage			93.1%,
Model fit	Hosmer and Lemeshow test		
Nagelkerke R^2		Chi-2	p
0.793		5.724	0.678

Table 2. *Logistic regression model predicting chess expertise based on the fractional dimension of the specific regions of interest (ROI), after controlling for age, sex, and education.The significance of the factors (p-values) and 95% confidence intervals (95% CI) of the B values are indicated based on 5000 bootstrap samples. SE, standard error; 8BM, caudal part of the dorsomedial prefrontal cortex; FOP5, frontal operculum OP5; PFt, inferior parietal lobule with a thin cortical ribbon; TF, temporal area F.*

4.3.4 Gyrification Index

We do not find significant differences between the GI of professional chess players and novices after correcting for multiple comparisons. Given that the GI distribution is normal in all ROIs, we performed two-sample t-tests showing significant differences in 11 ROIs listed in Table S2. These ROIs were introduced into the LR model after controlling for the effects of age, sex, and education. The resulting LR model shows that GI is predicted by two ROIs, the posterior part of the right anterior cingulate cortex (24 prime, a24pr) and the superior and posterior part of the right superior temporal sulcus (STSdp and STSpr), as reported in Figure

4 and Table 3. The accuracy of the model is good [efficiency = 69%, AUC = 0.798 (SE = 0.058, 95% CI = 0.685 to 0.911)].

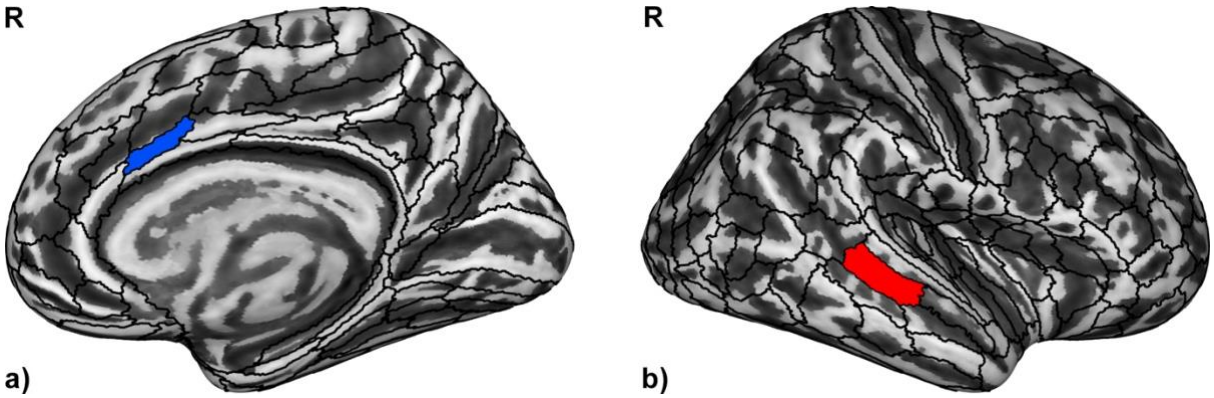

Figure 4. *Increased gyrification index in (**a**) the posterior part of the right anterior cingulate cortex (a24pr, in red) and decreased in (**b**) the superior and posterior part of the right superior temporal sulcus (STSdp, in blue) predicted chess expertise using logistic regression. R, right.*

Predictors with Bootstrap						
Predictors	**B**	**Bias**	**SE**	***p***	**95% CI**	
					Lower	**Upper**
Education	1.04	0.19	0.95	0.106	−0.27	3.00
Age (years)	0.04	0.01	0.07	0.367	−0.05	0.18
Male/female	−0.10	−0.01	0.19	0.441	−0.48	0.24
ROIs						
Right a24pr	−0.37	−0.08	0.26	0.007	−0.95	−0.09
Right STSdp	0.55	0.14	0.44	0.007	0.20	1.46
Intercept	−5.64	−2.13	13.46	0.503	−34.00	11.46
	Classification table					
		Predicted				
Observed	Novices	Professional chess masters		Correct %		
Novices	21	8		72.4%		
Professional chess masters	10	19		65.5%		
Overall percentage				69.0%		
Model fit	Hosmer and Lemeshow test					
Nagelkerke R^2		Chi-2		p		
0.359		7.030		0.533		

Table 3. *Logistic regression model predicting chess expertise based on the gyrification index of the specific regions of interest (ROI), after controlling for age, education, and sex.*
The significance of the factors (p-values) and 95% confidence intervals (95% CI) of the B values are indicated based on 5000 bootstrap samples. SE, standard error; a24pr, posterior part of the right anterior cingulate cortex; STSdp, superior and posterior part of the right superior temporal sulcus.

4.4 Discussion

This study investigated differences in surface-based cortical measures assessed with FD and GI in whole brain areas parcellated using the HCP atlas in 29 chess experts and 29 novices. We find that experts show an increase in FD in the left FOP5, which is correlated with the starting age of chess training, and a decrease in FD in the right SPL-7 m area, with a trend for a negative correlation between FD and the duration of daily training. When applying a logistic regression model, FD predicts chess expertise in a network of transmodal association regions, including the SPL-7 m and lateral temporal cortex in the right hemisphere and the fronto-opercular cortex FOP5, fronto-medial cortex 8BM, and IPL-PFt in the left hemisphere. Age, but not gender and education, have a significant effect on the model. Regarding GI, we find no significant differences between the two groups, after correction for multiple comparisons. Nevertheless, when using GI values from ROIs with significant differences in experts, chess expertise is predicted by two areas: the posterior part of the right anterior cingulate cortex and the posterior part of the right STSdp.

We find that chess experts have increased FD in the left FOP5, this region lies in the precentral part of the frontal operculum, rostrally to BA44. Although the role of FOP5 has not been fully explored, the frontal operculum is an important component of the attentional and memory circuits. For instance, this region is more active in professional musicians when simulating or imagining playing a well-known piece (retrieval of motor memory) (Lotze et al., 2003). FOP5 is also implicated in visuomotor learning, the selection of competing alternatives, and the retrieval and maintenance of rules, specifically when they are related to the context or when the subject is required to keep in mind a set of rule contingencies (Bunge, 2004). Moreover, increased performance in the executive component of a task is correlated with increased activation of the lateral frontal operculum (León-Domínguez et al., 2015) and can contribute to the transition from default mode to a task-positive network (Braver & Barch, 2006). More recently, FOP5 has been identified as a region of the extended multi-demand cognitive network, implicated more in relational tasks than in math and working memory tasks (Assem

et al., 2020). This is the first time that neural changes in this region are associated with chess expertise. FOP5 may be involved in various complex cognitive tasks, including the maintenance of multimodal mental representations that can promote high cognitive efficiency in chess experts. In particular, the level of player expertise, measured by the age of starting chess training, is positively correlated with the left FOP5 FD. These findings are in line with the previous literature that reveal that intensive training and learning processes produce changes in neurogenesis, glial genesis, and remodeling of different cellular and vascular components of the brain, resulting in regional structural and functional reorganization (Zatorre et al., 2012), especially from childhood to adulthood (Sydnor et al., 2021). The higher complexity in the left frontal operculum could reflect an increased processing effort in this area during chess playing. Since the frontal operculum is a phylogenetically old area that underlies several complex multimodal cognitive processes, when challenged, it cannot hyperspecialize. Thus, to maximize its efficiency, its complexity is increased.

Area 7 m is a heteromodal associative region located in the superior parietal lobule and the precuneus (Glasser et al., 2016). Specifically, the superior parietal lobule is known to mediate several functions related to spatial processing, such as spatial attention, remapping of attentional priorities, and mental rotation (Caspari et al., 2017). It also plays an important role in the integration of visual and motor information, which is important for visually guided actions (Wang et al., 2015). Moreover, area 7m is involved in the manipulation of information in working memory (Koenigs et al., 2009). Thus, SPL could be involved in chess skills for its role in spatial visual processing, spatial attention, and working memory (Wang et al., 2015). Area 7m plays a central role in a variety of integrated tasks, such as visuospatial imagery, memorization, and temporal processing of multiple task timelines (Cavanna & Trimble, 2006), and in mentalization and cognition. Moreover, the right precuneus is involved in controlling the spatial aspects of motor behavior (Seitz & Binkofski, 2003). Interestingly, as previously reported by Ouellette and colleagues, chess experts have cortical thinning in the left SPL and precuneus (Ouellette et al., 2020). Our study also shows a trend for an inverse correlation between cortical complexity in 7m and the duration of chess training. This suggests that

starting chess training in the middle of childhood may have enhanced cortical thinning, and this may lead to greater cognitive efficiency (Hänggi et al., 2014). Taken together, our findings suggest that a reduction in cortical complexity in the SPL and precuneus could be associated with better chess skills and performance, due to intensive cognitive training.

PFt is an association area located in the anterior part of the inferior parietal lobule that is mainly connected to the sensorimotor circuit. The PFt area has been reported to be a key node of a network that aims to generate purposeful hand actions in human and non-human primates (Borra et al., 2017). In particular, the left PFt is also considered a part of the so-called salience network (Seeley et al., 2007), directing attention to the most important stimuli in the environment. Interestingly, two studies also implicate IPL functional connectivity in chess experts. Both studies find a greater connectivity of IPL with the visuomotor network (Song et al., 2020) and the frontoparietal network (Wang et al., 2015) in chess experts that are correlated with the duration of professional chess playing. Consistent with our findings in area r7m, the reduced FD could reflect a higher specialization of this area after intensive training, producing a faster and more efficient processing of the chess moves.

Area TF is a limbic area of the lateral parahippocampal cortex located in the ventromedial part of the inferior temporal gyrus. TF is part of a large association network of regions including STS, visual area V4, and retrosplenial cortex, as well as multimodal association regions of the prefrontal, insular, cingulate, and posterior parietal cortices. Given its highly interconnected nature, area TF is highly engaged in tasks involving spatial information about the environment and, in particular, the processing of contextual associations (Aminoff et al., 2013) that support chess expertise through the holistic processing of various classes of stimuli. This is in line with an fMRI study showing that chess experts have increased activity in the collateral sulcus and the bordering area TF when looking at chess boards with plausible game positions, compared to boards where pieces were placed randomly (Bilalić et al., 2010). Consistently, a higher level of chess expertise is correlated with diffusion MRI connectometry in the bilateral ILF (Mayeli et al., 2018), an association white matter tract connecting the parahippocampal and extra-striate occipital cortices.

Area 8BM is the caudal part of the human dorsomedial prefrontal cortex that belongs to the core multi-demand cognitive network of regions. This network is activated by a broad domain of tasks integrating brain processing to access and bind information and cognition operations required for the complex behaviors that are required for chess playing (Assem et al., 2020).

Overall, chess expertise appears to be associated with cortical complexity changes in various regions engaged by tasks such as spatial information processing, mathematics, conceptualization, and social cognition. These findings suggest that the neural substrates involved in chess expertise can be defined within the broader framework of a network connecting transmodal and paralimbic association regions of the prefrontal, opercular, cingulate, dorsomedial parietal, and temporal cortices. In this view, FD appears to be a useful measure for a quantitative description of the structural complexity of the brain cortex, particularly in transmodal regions with flexible and high-level social and cognitive functions that are not well captured by CT measures. FD condenses cortex details into a single numeric value, which is an extremely compact measure of cortical complexity.

In particular, previous studies exploring FD in neurological disorders point toward the idea that a decrease in FD is associated with brain damage, yielding gray matter and few investigations show an increase of this measure in pathological conditions (Meregalli et al., 2022). Our findings of decreased FD in chess experts in right 7 m, right PF, left 8 bm, and left PFt suggest that reductions in FD in healthy subjects are not related to gray or white matter lesions, but can result from long-term and intense training that yields the refinement of association neural circuits via selective synaptogenesis and synaptic pruning.

Chess expertise is predicted by an increase in GI in the anterior part of the middle cingulate cortex and a decrease in GI in the superior and posterior part of the STS (Caspari et al., 2017). These are two key regions of the theory of mind network (Rilling et al., 2004), which is responsible for the mental representation of others' intentions and expectations in social interactions, including the prediction of deceptive behaviors (Lissek et al., 2008) and the comprehension of the intentions of actions (Tettamanti et al., 2017). Specifically, STS is involved in social cognition and motor skills (Baker, C. M., Burks, J. D., Briggs, R. G., Stafford,

J., Conner, A. K., Glenn, C. A., ... & Sughrue, M. E., n.d.) and the cingulate cortex in mentalizing functions and in the response to the selection of cognitive output (Blanton et al., 2001), respectively. GI changes in these areas can reflect the ability to understand the implications of the position of each piece in the game and to decode the emotions of the opponent, select the appropriate response, and take advantage of it in the match strategy. We do not find an effect of chess training on GI. This is expected, as GI changes are reported to occur during pregnancy and the first years of infancy and to remain relatively stable throughout life (Blanton et al., 2001).

Cortical complexity assessed with FD is altered in chess experts in two regions implicated in high-level cognitive tasks and modulated by chess training. Our findings extend the reports of altered CT in chess experts (Ouellette et al., 2020) to a more complex measure that can reflect the characteristics of chess training. In particular, chess expertise is associated with differences in FD in a set of transmodal association late-maturing regions that undergo structural and functional changes until early adulthood (Sydnor et al., 2021). Indeed, FD, unlike GI, is likely to change in response to cognitive demands throughout life (Blanton et al., 2001), and its changes can contribute to the performance of complex cognitive behaviors, including chess expertise. However, more research is needed to assess whether FD can be a reliable method to investigate cortical changes related to expertise.

Lastly, we also investigated CT in chess players and novices and found widespread cortical thinning in frontoparietal and visual areas involving primary, unimodal, and heteromodal areas. Our results replicate the findings reported by Ouellette and colleagues [8]. Of note, Ouellette et al. [8] investigated CT in the same dataset but using a different processing tool, Freesurfer versus CAT12, and a different cortical parcellation atlas, indicating that our results were not influenced by the processing steps that were used to estimate CT.

Furthermore, a series of studies investigated the neural correlates of chess expertise using the same dataset, although focusing on resting-state connectivity and brain volumetry. In one study that investigates the dynamic resting state functional connectivity, the chess masters show enhanced global dynamic fluidity, operating over an extended dynamic range [66].

Another resting state study shows increased functional connectivity between the posterior fusiform gyrus and the visuospatial attention and motor networks in chess players (Song et al., 2020). A surface-based study of cortical thickness by Ouellette and colleagues reports cortical thinning in professional chess players in the left SPL and precuneus (Ouellette et al., 2020). Finally, only a VBM study is performed in this dataset and finds a significant reduction in the thalamic volume in chess masters, and this volume is correlated with the level of chess expertise and the training time (Wang et al., 2015). In our study, we analyze the complexity of cortical folding, a surface-based index, which is complementary to other morphometric approaches in the identification of structural changes in the cortex (Meregalli et al., 2022). In particular, cortical complexity summarizes information from different gray matter components, thus, resulting in a greater ability to detect changes associated with brain aging, cognition, and neuropsychiatric disorders, including those associated with cognitive impairment compared to the traditional surface- and volume-based approaches (Meregalli et al., 2022). Thus, our findings extend previous results of structural changes in the thalamus and parietal cortex to a broader structural network, including prefronto-tempo-parietal regions, which is consistent with the functional results indicating increased overall brain dynamics and functional connectivity in parieto-temporal networks, which may underlie the spatial information processing, working memory, conceptualization, and mentalization that can be necessary to become a chess master.

Some limitations must be acknowledged. The sample size of this study is small. However, the study is sufficiently powered to identify group differences for morphometric measures, as confirmed by previous studies on the same database (K. Li et al., 2015). Another limitation is the type of phenotypic characterization of the participants that is limited to measures of demographic and chess expertise, which is sufficient for the purpose of the study, but hinders the possibility of investigating specific cognitive skills. Future studies incorporating thorough neurocognitive measures are needed.

This study investigated the neural basis of chess expertise by exploring the differences in FD and GI in chess experts and novice participants. We show that chess expertise is associated

with FD changes in a flexible and interactive network of transmodal areas that integrate visuospatial information, working memory, abstraction, mentalization, and social cognition functions that promote the development of high-level skills and confer advantages to chess experts over novices. These findings add to previous evidence that the neural bases of chess expertise are related to a network of transmodal regions with a functional organization influenced by a variety of developmental, structural, and environmental factors (Sydnor et al., 2021). This study also emphasizes that brain processes can be explored using cortical complexity assessed with FD. Future studies with larger sample sizes and more detailed cognitive information will allow a better and more in-depth understanding of the neural substrates of chess playing. We also suggest that studying the brain structure of chess players longitudinally would shed light on the nature of FD changes and their ontogenetic processes. Future research should also investigate the effects of extensive cognitive training on brain structure, not only due to chess play but also due to the learning of complex cognitive skills. Furthermore, longitudinal studies aimed at identifying brain areas that mediate complex cognitive skills in learning, including mastering chess, could be useful for a better understanding of learning and for the use of neurostimulation techniques to improve this process.

Chapter 5

5. General Discussion

In recent years, advances in computational methods have greatly improved the study of the cerebral cortex, enabling researchers to analyze its structure within various contexts, including physiological (such as neurodevelopment and aging) and pathological (such as neurological and psychiatric conditions).

The main goal of this work is to examine the cortical complexity of the human cortex in different samples, both in pathological and healthy populations.

5.1 Summary of main findings

5.1.1 Study 1

Cortical complexity (CC) and its associated measure (FD) were reduced in schizophrenia patients compared to healthy controls in the right superior temporal gyrus. Previous research has linked this region, which plays a key role in auditory and language processing, to auditory verbal hallucinations, and our findings support this association. Bipolar disorder patients showed significantly lower CC in the left pars opercularis compared to healthy controls, which is consistent with previous research finding reduced cortical thickness in this region. Additionally, BD patients had increased FD in the left lingual gyrus and this measure was positively correlated with the Brief Psychiatric Rating Scale (BPRS) mania score. When compared to schizophrenia, BD patients showed significant increases in FD in the left inferior temporal gyrus, lLG, right temporal pole, inferior and superior temporal cortex.

5.1.2 Study 2

This study compared the cortical complexity between patients with cocaine addiction and healthy controls, and correlated it with characteristics of addiction and impulsivity. The results showed that patients with cocaine addiction had higher levels of impulsivity and reduced CC in a cluster encompassing the left insula and supramarginal gyrus, as well as in the left medial orbitofrontal cortex. Additionally, the CC in the left medial orbitofrontal cortex was correlated with the age of onset of cocaine addiction and with attentional impulsivity. These findings suggest that chronic cocaine use may be associated with changes in the cortical surface in fronto-parieto-limbic regions involved in emotional regulation, and that these changes may be linked to earlier use of cocaine.

5.1.3 Study 3

For this study, we used structural magnetic resonance imaging data from 29 chess experts and 29 novice players. We compared the CC of different brain regions between the two groups and used a multivariate model to identify surface-based brain measures that could predict chess expertise. The results showed that in chess experts, the CC was increased in the left frontal operculum and correlated with the starting age of chess practice, and decreased in the right superior parietal lobule. Chess expertise, also investigated through a logistic regression model was indeed predicted by the CC in a network of fronto-parieto-temporal regions. These findings suggest that the complex properties of the brain surface in a network of transmodal association areas important for flexible high-level cognitive functions are important for chess expertise, and that these changes may develop over time with long-lasting practice.

5.2 Cortical complexity, psychiatric disorders, cognition and behavior

For the purposes of this work, we chose to evaluate the cortical complexity in both healthy and clinical populations, as CC appears to provide valuable morphological information beyond what is captured by other indices such as cortical thickness, local GI, and cortical surface (Meregalli et al., 2022).

Psychiatric diseases, such as schizophrenia and bipolar disorders (investigated in Study 1), are defined by a partly shared genetic risk, but also share environmental attributes, including prenatal factors and substance misuse (Heinz et al., 2013). Both disorders are also characterized by an overlap of clinical symptoms, including alterations of thought, emotion, behaviors, perception and also cognition (Murray et al., 2004). Indeed, bipolar disorder and schizophrenic patients also share impairments in many cognitive domains, including attentions, memory and executive functions (Daban et al., 2006). Due to all these similarities and the broad range of symptoms that are influenced these disorders, it is necessary to implement precise and reliable neuroimaging methods that can help us better differentiate the two disorders, especially in the first stages of the illness. In our line of work, we argue that cortical complexity, and the fractal dimension (its associated value), could be an innovative approach to identify distinct psychopathological phenotypes and their neurobiological processes. We showed how schizophrenics patients a reduction in cortical complexity in the right superior temporal gyrus, when compared to both healthy controls and bipolar disorder patients and how this reduction in CC was correlated with a particular symptom, the severity of hallucinations. There have been already previous findings that associated grey matter abnormalities of the superior temporal gyrus with auditory hallucinations, especially considering that this area has a key-role in auditory and language processing (Sun et al., 2009). On the other hand, bipolar patients displayed reductions in cortical complexity, when compared to schizophrenic patients and healthy controls, in the left pars opercularis. This reduction in CC was also associated with working memory deficits. The role of the left pars

opercularis in the working memory is well explored by the literature (Metzler-Baddeley et al., 2016), and our research strengthen the association between this area and the working memory domain thanks to the investigation of the cortical complexity. Furthermore, we also discovered an area of increased CC in the right lingual gyrus in bipolar patients, and its association with manic symptoms. This is in line with previous findings, where grey matter volumes of this region where also increased when compared to an healthy population (Wise et al., 2017) and manic symptoms ratings (Kim et al., 2020).

In Study 1 we hypothesized how alteration in CC may act as a biomarker for psychiatric disorders. We noticed also how alteration of the cortex structure was also correlated to change in behaviors (hallucinations severity and manic symptoms) and in cognition (working memory deficits). We then decided to further investigate these aspects by investigating another clinical population, patients with substance use disorders in Study 2. This population is usually characterized by deficits in behaviors, specifically in impulse control (de Wit, 2009), and in cognition, with impairments in attention (Anderson et al., 2013). Specifically, attentional impulsivity has been reported to correlate negatively with the volume of the orbitofrontal cortex in psychiatric patients with impulsive behaviors. (Matsuo et al., 2009). The objective of Study 2 was to further investigate this associations by applying cortical complexity analysis in patients with cocaine addiction. We found that this clinical population, compared to healthy controls, showed lower CC in the left insula, supramarginal gyrus and the orbitofrontal cortex. The orbitofrontal cortex, in particular, appears to be a crucial player in the addiction development, with its role in decision-making and goal-oriented-behavior (Volkow & Fowler, 2000). Indeed, in our study, the decline in CC of the orbitofrontal cortex was correlated with the age of onset of cocaine use, suggesting a dose-effect interaction between cocaine use and the cortex organization. Furthermore, consistently with previous studies (Hulka et al., 2015), cocaine addict patients showed significantly higher attentional impulsivity, when compared to controls. Interestingly, we found that the complexity of the orbitofrontal cortex was also associated with the attentional domain of the BIS scale. This particular finding could suggest that cocaine use could induce brain changes that contribute to the reinforcement of

the addictive behavior. Even more, we reported a reduction of cortical complexity in the left insula. Notably, the insula play an important role in addiction (Battistella et al., 2014), including cannabis, online gaming addiction, social media and smoke. Structural alteration in the insula may affect the interaction between affective and cognitive processes in decision making, leading to the lack of avoidance responses to events that ultimately bring the subject to pursue drug-seeking behavior and craving. Finally, we reported reduced cortical complexity also in the supramarginal gyrus, an area that had been previously reported to reflect reduced grey matter volumed in cocaine addicts (Barrós-Loscertales et al., 2011). These results show that cortical complexity analysis, measured by the fractal dimension, is indeed altered in cocaine addiction. We support the idea that the development of this addiction may be associated with neurobiological alterations that underlie the vulnerability to this disorder. Then, cocaine use, that is led by this vulnerability, can affect the neural circuits that mediate behavior which support the addiction process itself, with a feedforward mechanism. In this study (Study 2), we further investigated how cortical complexity analysis can led us to a better understanding of behaviors and symptomatology in psychiatric disorders such as substance abuse disorders, but also how certain substances and behaviors can have an active effect on the structure of the cortex. Up until now, we have reported how psychiatric diagnosis and substances could have an effect on the cortical structure, measured by a solid methods such as the fractal dimension.

Stemming from this, in the final study, Study 3, we wanted to further investigate this brain-behavior relation by investigating the cortical structure of a population that is not characterized by mental disorders. Our objective was to understand if the cortical complexity indexes could be influenced by behaviors, without the effects of diagnosis or external substances. For this reason, we chose to investigate chess masters, comparing them to chess novices. The chess game is a complex intellectual activity that provides a useful model for the study of memory and attention (Charness, 1992). Both memory and attention have been proved by our previous studies (Study 1 and Study 2) to be connected to an alteration of the cortical structures. We found that chess experts have increased cortical complexity in a region of the left frontal

operculum. This region is an important component of the attentional and memory circuits. In fact, it is more active in professional musicians when simulating/imagining playing a musical piece, thus via the retrieval of motor memory (Lotze et al., 2003). The frontal operculum is also important for visuomotor learning, the selection of competing alternatives and the retrieval and maintenance of rules, specifically when the subject is required to keep in mid a set of rule contingencies (Bunge, 2004). Importantly, we found that the level of player expertise, measured by the age of starting chess training, is positively correlated with the cortical complexity values in this region. This finding is in line with previous literature that investigate how intensive training and learning processes produce changes in regional structural reorganization (Zatorre et al., 2012). This higher cortical complexity in the left frontal operculum could reflect an increased processing effort in this area during chess playing. Since the frontal operculum is a phylogenetically old area that underlies several complex multimodal cognitive processes, when challenged, it cannot hyperspecialize. Thus, to maximize its efficiency, its complexity is increased. Furthermore, we found a decrease in cortical complexity in an area of the right superior parietal lobule, area 7m. Specifically, the superior parietal lobule is known to mediate several function related to spatial processing, such as spatial attention, remapping of attentional priorities and mental rotation (Wang et al., 2015). Moreover, this area is also associated with the manipulation of information in working memory (Koenigs et al., 2009). Interestingly, a previous study on the same participants revealed that this area was characterized by cortical thinning (Ouellette et al., 2020). Our study also shows a trend for an inverse correlation between cortical complexity in 7m and the duration of chess training. This could suggest that starting chess training in the middle of childhood may have enhanced this reduction in cortical complexity, and this may lead to greater cognitive efficiency. Finally, we investigated how the cortical complexity was predicted, by a logistic regression mode, in a network of fronto-parieto-temporal regions. Overall, it appears that chess expertise is related to changes in cortical complexity in various regions involved in tasks such as spatial information processing, mathematics, conceptualization, and social cognition. These findings suggest that the neural substrates underlying chess expertise can be identified within a

network connecting transmodal and paralimbic association regions in the prefrontal, opercular, cingulate, dorsomedial parietal, and temporal cortices. In this context, FD appears to be a useful measure for quantitatively describing the structural complexity of the brain cortex, particularly in transmodal regions with flexible, high-level social and cognitive functions that are not well captured by measures of cortical thickness. FD condenses detailed information about the cortex into a single numerical value, making it a highly compact measure of cortical complexity. We have previously reported how, in certain conditions such as psychiatric disorder or substance use, cortical complexity is altered in certain population, but thanks to further investigating healthy populations, we can hypothesizes that that reductions in cortical complexity are not necessary limited or related to gray or white matter lesions, but can result from long-term and intense training that yields the refinement of association neural circuits via selective synaptogenesis and synaptic pruning.

5.3 Limitations of the studies

In Study 1, the use of a cross-sectional design to investigate the cortical alterations underlying bipolar-schizophrenic spectrum disorders, limits the ability to make causal inferences. Limitations arise due to the inability of a cross-sectional design to distinguish between cause-and-effect relationships. This design only provides information about associations between variables at a specific point in time. Furthermore, the use of pharmacological treatments is a potential confounding variable in this type of study. To account for this, we explored the potential impact of medications on brain structure and found no effect of medications on cortical complexity. However, the possibility remains that medication use could affect, in a more indirect way, the brain structure. Therefore, these results should be interpreted with caution, and future research using other study designs, such as longitudinal studies, is needed to better understand the relationship between medications and brain structure.

The aim of Study 2 was to investigate the cortical complexity in patients with cocaine addiction. One of the limitations of this study was its relatively small sample size, which consisted of only men. This limitation may limit the generalizability of the results to women. However, it is important to acknowledge that addiction in general, and cocaine addiction in particular, present several differences between sexes. These differences may include the severity of craving, medical and psychiatric comorbidity, and social, family, and employment problems. By including only men, the heterogeneity of the sample was reduced, potentially resulting in more robust findings. Nevertheless, it is crucial to recognize that the cross-sectional design of the study is insufficient to establish causal relationships between brain changes and substance use disorder. A longitudinal study design would allow for the examination of changes in cortical folding over time, providing insights into the directionality of the relationship between brain changes and substance use disorder. In conclusion, the limitations of the sample size and cross-sectional design of Study 2 should be taken into consideration when interpreting the results, and future research should aim to address these limitations to gain a more comprehensive understanding of the relationship between cocaine addiction and cortical folding.

Study 3, which aimed to investigate the neural correlates of chess expertise, has some limitations that must be acknowledged. One of the limitations is the small sample size used in this study. Despite this limitation, the study was able to identify group differences for morphometric measures, as confirmed by previous studies on the same dataset. It is important to consider the impact of sample size on the study's power, as larger sample sizes may increase the power of the study and the generalizability of the results. However, it is important to note that the population of chess masters is extremely small, and so it is difficult to recruit large numbers of participants for a study of this nature. Another limitation of the present study is the type of phenotypic characterization of the participants, which is limited to measures of demographic and chess expertise. While this characterization is sufficient for the purpose of the study, it hinders the possibility of investigating specific cognitive skills that may be relevant

to chess expertise. As such, future studies may benefit from a more comprehensive characterization of participants that includes measures of cognitive abilities beyond those related to chess expertise. For example, future studies may benefit from including measures of memory, attention, and problem-solving abilities, which are critical components of chess expertise.

Overall, while the present study has some limitations, such as the small sample size and limited phenotypic characterization, it provides valuable insights into the neural correlates of chess expertise. Future studies should aim to address these limitations to further elucidate the neural mechanisms underlying expertise in chess and related cognitive skills. By doing so, we may gain a more comprehensive understanding of the neural basis of expertise and its potential implications for cognitive development and rehabilitation.

5.4 Conclusions and future directions

Cortical complexity and its associated measure, the fractal dimension (FD), is a useful method for capturing additional morphological information of the cortex. Compared to other cortical indices, such as cortical thickness and gyrification index, FD is especially valuable in capturing unique features of the cortical structure. By incorporating FD measurements into structural evaluations of the cortex, researchers may gain deeper insights into cortical morphology that cannot be obtained through other means. Despite its usefulness, FD has not yet been systematically used in the evaluation of cortical structure. This underutilization highlights the need for further research to explore the potential benefits of including FD measurements in structural assessments of the cortex. Ultimately, a more comprehensive approach that integrates FD with other cortical indices may provide a more complete understanding of the complexities of cortical structure and function. Further longitudinal studies utilizing FD are needed to understand the role of cortical complexity during various neurodevelopmental

stages and aging, as evidenced by the lack of such observations in the existing FD literature. Such studies would enable us to gain a better understanding of the structural changes in the cortex over time, which would aid in the identification of neural mechanisms underlying neurological and psychiatric disorders. Additionally, the data obtained from longitudinal studies would allow for the assessment of the effectiveness of interventions aimed at a better understanding of cortical structure and function. Therefore, I believe that a certain priority in the field would be to conduct longitudinal studies that utilize FD to investigate cortical complexity in both clinical and general population.

Chapter 6

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