

The dynamics of cerebro-cerebellar resting-state functional connectivity: relation to cognition, behavior, and pathophysiology

Majd Abdallah

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DOCTEUR DE L'UNIVERSITÉ DE BORDEAUX

ÉCOLE DOCTORALE Sciences de la Vie et de la Santé

SPÉCIALITÉ **Neurosciences**

Par Majd ABDALLAH

The Dynamics of Cerebro-Cerebellar Resting-State

Functional Connectivity: Relation to Cognition,

Behavior, and Pathophysiology

Sous la direction de Dr. Sandra CHANRAUD

Soutenue le 29 Septembre 2020

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La dynamiques de la connectivité fonctionnelle cérébro-cérébelleuse au repos: relation avec la cognition, le comportement et la physiopathologie

Résumé

La connectivité fonctionnelle à l'état de repos (CF), mesurée avec l'imagerie par résonance magnétique fonctionnelle (IRMf), a mis en évidence des connexions fonctionnelles entre le cervelet et les régions cognitives du cerveau, qui a soutenu un rôle important pour le cervelet dans la cognition. Ces résultats ont été basés sur des mesures statiques de la CF. Cependant, il s'agit d'une approche simpliste du CF qui a récemment été remise en question, les résultats indiquant la présence d'une dynamique continue et non aléatoire dans le CF à de courts intervalles de quelques secondes, ce qui, étant donné la nature dynamique du cerveau, est une vision plus naturelle qui peut coder des informations sur des fonctions cognitives complexes. Jusqu'à présent, le cervelet a été négligé dans la plupart des études sur la CF dynamique, malgré son rôle bien reconnu dans les fonctions cognitives complexes. Dans cette thèse, nous avons émis l'hypothèse que la dynamique du cervelet au repos peut être significative, en saisissant des aspects de la cognition et du comportement non pris en compte par le cervelet statique et en présentant des altérations des troubles cérébraux associés au dysfonctionnement cérébro-cérébelleux, comme l'alcoolisme. Nous avons testé ces hypothèses dans deux études distinctes portant sur la dynamique de la CF cérébro-cérébelleuse en relation avec des traits complexes, tels que l'impulsivité (première étude) et l'alcoolisme (deuxième étude). La première étude a été motivée par une hypothèse récente sur le rôle du cervelet dans l'impulsivité, un trait de personnalité complexe défini comme la tendance à agir sans prévoyance. Nous avons émis l'hypothèse que les différences individuelles dans les traits normaux d'impulsivité pouvaient être associées à la force (statique) et à la variabilité temporelle (dynamique) du CF cérébro-cérébelleux. Nous avons testé cette hypothèse en utilisant des données d'IRMf à l'état de repos et des auto-rapports d'impulsivité (UPPS-P et BIS/BAS) d'un groupe d'individus en

bonne santé (N=134). En particulier, nous avons utilisé des techniques robustes pour identifier les réseaux cérébraux et cérébelleux, calculer des mesures sommaires de la CF statique et dynamique, et tester les associations avec l'impulsivité. Nous avons observé des preuves liant de multiples formes d'impulsivité à la force et à la variabilité temporelle de la CF au repos entre le cervelet et un ensemble de réseaux cérébraux dynamiques et intégratifs qui soutiennent le contrôle cognitif et les processus de récompense, ce qui soutient notre hypothèse selon laquelle la dynamique de la CF cérébro-cérébelleuse est pertinente sur le plan comportemental. Dans la seconde étude, nous avons émis l'hypothèse que la dynamiques de la CF cérébro-cérébelleuse différerait entre les les patients alcooliques et les contrôles, en particulier dans les circuits frontocérébelleux. Pour tester cette hypothèse, nous avons exploré les différences de dynamiques de la CF cérébro-cérébelleuse entre un groupe de patients alcooliques (N=18) et un groupe de contrôles (N=18), en comparant des groupes sur différentes mesures de connectivité dynamique. Les résultats ont révélé une altération de la dynamique du réseau fonctionnel cérébrocérébelleux chez les sujets alcooliques, caractérisée par une hypervariabilité de la CF dans les réseaux fronto-parieto-cérébelleux, une réduction de la flexibilité cérébelleuse et une augmentation de l'intégration cérébelleuse. Ces résultats suggèrent un rôle possible de la dynamique des réseaux fronto-pariétal-cérébelleux dans la physiopathologie de ce trouble. Pris ensemble, les résultats de cette thèse soulignent l'utilité de compléter les approches statiques de la CF par une analyse dynamique de la CF pour approfondir notre compréhension du fonctions des réseaux cérébro-cérébelleux et les neurobiologie des comportements complexes et les troubles du cerveau.

Mots clés: Imagerie par Résonance Magnétique Fonctionnelle, Connectivité Fonctionnelle Dynamique, Cervelet, Connectivité fonctionnelle Dynamique Cérébro-Cérébelleux, Cognition, Comportement

The dynamics of cerebro-cerebellar resting-state functional connectivity: Relation to cognition, behavior, and pathophysiology

Abstract

Studies of resting-state functional connectivity (FC), measured by functional magnetic resonance imaging (rsfMRI), have revealed extensive functional connections between the cerebellum and association regions in the brain, supporting an important role for the cerebellum in cognition. These findings have been based on static FC measures averaged across entire scans spanning a few minutes. However, this is a narrow view that has been recently challenged, with findings pointing to the presence of an ongoing, behaviorally relevant dynamics in resting-state FC occurring at short timescales of a few seconds, which, given the dynamic nature of the brain, is a more natural view that may encode information about complex cognitive functions. So far, however, the cerebellum has been overlooked in most, if not all, studies of dynamic FC, despite its well-recognized role in coordinating complex cognitive functions. In this thesis, we hypothesized that the dynamics of cerebro-cerebellar FC, during rest, may be behaviorally relevant, capturing aspects of cognition and behavior not accounted for by static FC and exhibiting alterations in brain disorders commonly associated with cerebro-cerebellar dysfunction, such as alcohol use disorder (AUD). We tested these hypotheses in two separate studies focusing on the dynamics of cerebro-cerebellar FC in relation to complex traits and disorders, such as impulsivity (first study) and AUD (second study). The first study has been motivated by a recent hypothesis for a role of the cerebellum in impulsivity; a complex personality trait defined as the tendency to act without foresight. We hypothesized that individual differences in normal impulsivity traits could be associated with the (static) strength and (dynamic) temporal variability of cerebro-cerebellar resting-state FC. We tested this hypothesis using rsfMRI data and self-report questionnaires of impulsivity (UPPS-P and BIS/BAS) collected from a group of healthy individuals. In particular, we employed data-driven techniques

to identify cerebral and cerebellar resting-state networks, compute summary measures of static and dynamic FC, and test for associations with self-reported impulsivity. We observed evidence linking multiple forms of impulsivity to the strength and temporal variability of resting-state FC between the cerebellum and a set of highly dynamic and integrative brain networks that support top-down cognitive control and bottom-up reward/saliency processes, supporting our hypothesis that cerebro-cerebellar FC dynamics are behaviorally relevant. In the second study, we hypothesized that the dynamics of cerebro-cerebellar FC at short timescales would differ between AUD and controls, especially in the frontocerebellar circuits. To test this hypothesis, we explored the differences in the dynamic cerebro-cerebellar FC between an AUD group (N=18) and a group of unaffected controls (N=18) by comparing groups on different dynamic connectivity measures. Results revealed altered cerebro-cerebellar FC dynamics in the AUD group characterized by hypervariability of FC within fronto-parieto-cerebellar networks, reduced cerebellar flexibility, and increased cerebellar integration, compared with controls. These results suggest a possible role for the dynamics of fronto-parieto-cerebellar networks in the pathophysiology of this disorder. Taken together, the findings from this thesis highlight the utility of complementing static FC approaches with dynamic FC analysis in furthering our understanding of the functional repertoire of cerebro-cerebellar networks and the neurobiological architecture of complex behaviors and brain disorders.

Keywords: Cerebellum, Dynamic Functional Connectivity, Cerebro-Cerebellar Networks, Resting-State fMRI, Cognition

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Declaration of Authorship

I, Majd ABDALLAH, declare that this thesis titled, "The Dynamics of Cerebro-Cerebellar Resting-State Functional Connectivity: Relation to Cognition, Behavior, and Pathophysiology" and the work presented in it are my own. I confirm that:

- This work was done wholly while in candidature for a doctoral degree at the University of Bordeaux, France.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have literally quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

"Only a few know, how much one must know to know how little one knows."

Werner Heisenberg

To my parents, my friends, and the people I love

Many of us pave their own paths in life, education, career, and research with failures, improvisations, hard work, and sleepless nights filled with endless ruminations and self-doubts. However, no one is truly able to get somewhere without the help, support, and opportunities provided by mentors, peers, family, and friends who all deserve a credit for their efforts. First, I wish to express my sincere appreciation and gratitude to my supervisors, **Dr. Sandra Chanraud** and **Dr. Nicolas Farrugia**, who have given me a great opportunity to pursue a doctorate degree in neuroscience and have been supportive and patient enough to see me at the finish line after almost four years. Second, the financial support provided by the **Translational Research and Advanced Imaging Laboratory** (TRAIL), within the context of the "Laboratory of Excellence" (LabEx) project, is very much appreciated. Without their support and funding, this thesis could not have been started nor completed.

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List of Abbreviations

AUD	Alcohol Use Disorder
BAS	Behavioral Approach System
BGN	Basal Ganglia Network
BIS	Behavioral Inhibition System
BOLD	Blood Oxygen Level Dependent
CCAS	Cerebellar Cognitive Affective Syndrome
CON	Cingulo-Opercular Network
CSF	CerebroSpinal Fluid
DAN	Dorsal Attention Network
DMN	Default Mode Network
ECN	Executive Control Network
FC	Functional Connectivity
fMRI	functional Magnetic Resonance Imaging
FO	Fractional Occupancy
FPN	Fronto-Parietal Network
FSN	Frontal Salience Network
GICA	Group Independent Components Analysis

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GIG-GICA	Group Information Guided—Group Independent Components Analysis
GM	Gray Matter
HMM	Hidden Markov Models
IC	Independent Component
maxFO	Maximum Fractional Occupancy
meanFD	Mean Framewise Displacement
MRI	Magnetic Resonance Imaging
pCun/PCC	Precuneus and Posterior Cingulate Cortex
RN	Reward Network
RSN	Resting-State Network
rsfMRI	Resting-State Functional Magnetic Resonance Imaging
SN	Salience Network
TR	Repetition Time
TVFC	Time-Varying Functional Connectivity
UCT	Universal Cerebellar Transform
VAN	Ventral Attention Network
WM	White Matter

General Introduction

Brief Review: What Do We Know

Constituting 10% of the brain's total volume, the cerebellum contains roughly 80% of the neurons of the central nervous system, which is regarded as one of the mysteries of human evolution (Leiner, 2010). Until recently, the often forgotten "little brain" has been though of as a sensorimotor structure that is not involved in nonmotor, cognitive functions (Buckner, 2013). This entrenched belief has been partly driven by early observations of severe motor disturbances in patients with cerebellar damage and the lack of monosynaptic projections between the cerebral cortex and the cerebellum, which precluded any investigation into the cerebellum's full organizational properties (Buckner, 2013). Yet, the view of the cerebellum as sensorimotor regulator has not helped in solving the mystery of the dramatic enlargement of the cerebellum's posterolateral regions and the deep nuclei embedded in cerebellar white matter in the human brain relative to other primates (Leiner, 2010). One speculation has been that a more complex sensorimotor map with novel properties and functions may occupy these "extra large" regions of the cerebellum. However, the past three decades have witnessed an accumulation of evidence implicating the cerebellum in a wide array of functions that extend beyond the motor field to encompass almost every other function of the brain. These functions include posture and balance, movement coordination, cognitive control, abstract thinking, and inferring on others' mental state or beliefs (Schmahmann, 2019; Sokolov, 2018).

Evidence of a possible cerebellar role in cognition can be attributed to the use of novel trans-synaptic viral tract tracing techniques, which can delineate polysynaptic connections. In this domain, studies have uncovered anatomically segregated closed-loop connections between the cerebellum and higher-order cognitive regions 2

of the brain, most notably the prefrontal cortex, that do not overlap with previously detected sensorimotor connections, suggesting a non-motor involvement of the cerebellum (Middleton and Strick, 1994). Other equally important evidence of cerebellar contributions to cognition has come from clinical observations of cognitive and affective disturbances in patients with lesions in the posterolateral parts of the cerebellum (Schmahmann and Sherman, 1997). These observations culminated in the introduction of the "Cerebellar Cognitive Affective Syndrome" (CCAS; also known as Schmahmann's syndrome, Schmahmann and Sherman, 1997) and the theories of the universal cerebellar transforl (UCT) and the Dysmetria of thought. These theories hold that the cerebellum performs unique computational processes across the motor and non-motor domains and that damage to cognitive cerebellar regions induce cognitive impairments characterized by loss of fluidity and coordination, in a similar manner to motor impairments caused by damage to the motor cerebellum (Schmahmann, 1998; Guell et al., 2017). In this context, Jeremy Schmahmann, one of earliest and most prominent proponents of the cerebellar involvement in non-motor functions, has hypothesized that, "It may also transpire that in the same way as the cerebellum regulates the rate, force, rhythm, and accuracy of movements, so may it regulate the speed, capacity, consistency, and appropriateness of mental or cognitive processes" (Schmahmann, 1991a). Thus, the postulated role for the cerebellum in cognition presides on the coordination of diverse streams of thoughts and information underlying a range of cognitive domains in a timely manner, thereby maintaining fluidly coordinated cognitive processing and facilitating the acquisition of new "mental skills" (Leiner, Leiner, and Dow, 1986; Sokolov, Miall, and Ivry, 2017).

Yet, the major breakthrough and direct evidence of a cognitive role for the cerebellum are attributed to the introduction of functional neuroimaging, especially functional magnetic resonance imaging (fMRI), which have provided the means to observe and visualize cognitive regions of cerebellum (Kim, Ugurbil, and Strick, 1994; Raichle et al., 1994). In this domain, researchers have unexpectedly detected activations in the cerebellum in response to cognitive and limbic tasks that are independent of any overt sensorimotor demand (Buckner, 2013; Stoodley, Valera, and Schmahmann, 2012; Van Overwalle et al., 2014). Moreover, by measuring the spontaneous low-frequency fluctuations in brain activity while subjects rested in an MRI machine without engaging in any task, neuroscientists have been able to map the complete functional network organization of the human cerebellum, with findings indicating that the majority of the cerebellum is functionally connected with well-known cognitive networks in the brain, notably the default mode, attention, salience and the executive control networks (Buckner et al., 2011; Guell et al., 2018). These studies have used the concept of functional connectivity, defined as the temporal correlation between remote neurophysiological events (i.e., neuronal signals, changes in oxygen level) recorded simultaneously in distinct brain regions. In fMRI, especially resting-state fMRI (rsfMRI) where subjects do not perform any explicit task, functional connectivity measures the synchronization between the levels of oxygen consumption, during the scan, in distinct brain regions as a proxy to neuronal activity and can be quantified with measures of statistical dependencies, such as Pearson's correlation. Thus, resting-state fMRI studies have found that the posterolateral regions of the cerebellum have strong functional connectivity with association regions in the brain, suggesting the involvement of the cerebellum in cognitive processing.

Apart from delineating functional regions in the cerebellum, many studies have used fMRI and functional connectivity to understand the role of the cerebellum and the cerebro-cerebellar functional networks in a growing number of brain disorders, such a substance addiction (Chanraud et al., 2013), schizophrenia (Zhuo et al., 2018), autism (Khan et al., 2015), and attention deficit/hyperactivity disorder (ADHD; Stoodley, 2016). The involvement of the cerebellum and its circuits within those disorders contributes to a broad range of executive and affective deficits that lead to symptoms such as behavioral disinhibition, hyperactivity, craving, compulsive and impulsive behaviors, poor performance on cognitive tasks, personality changes, and emotional distress (Schmahmann et al., 2019). Owing to the advent of resting- state fMRI, these findings, among others from task-activation experiments (King et al., 2019; Stoodley, Valera, and Schmahmann, 2012), have placed the cerebellum on the neurobiological map of a wide variety of cognitive functions and brain disorders, making it an important cognitive structure and a potential therapeutic target that should not be excluded from anatomical and functional models



FIGURE 1: A schematic summarizing the interactions between the cerebellum and higher-order association regions in the brain. The cerebellum receives input and sends output to association cortical areas in a bidirectional closed-loop network architecture. In addition, resting-state fMRI studies have revealed extensive cerebellum-based representations of the networks anchored within these association regions. Figure reproduced from Sokolov, Miall, and Ivry (2017), with permission.

of complex human behaviors.

Problem Statement and Hypothesis: What is Missing

The vast majority of findings on the functional organization of the human cerebellum have been based on the assumption of a "static" FC that does not vary across an entire fMRI scan. This approach has been pivotal for delineating the stable organization of networks in the brain (Damoiseaux et al., 2006; Yeo et al., 2011), including the cerebellum (Buckner et al., 2011). However, it is rather a narrow view that has been challenged over the past few years, with findings pointing to the presence of an ongoing, behaviorally relevant FC variations at faster timescales of a few seconds, which, given the dynamic nature of the brain, is a more natural view that might hold answers to fundamental questions about the function and dysfunction of the brain (Liégeois et al., 2019; Zalesky et al., 2014). As a response to the shortcomings of traditional measures of FC, the past decade have witnessed a growing interest in studying the fast variations in FC, commonly known as dynamic or timevarying FC (Calhoun et al., 2014; Preti, Bolton, and Ville, 2017; Lurie et al., 2020). Individual differences in both task-based and resting-state dynamic FC have been associated with cognitive task performance (Braun et al., 2015; Douw et al., 2016; Fong et al., 2019), attention (Fong et al., 2019), learning (Bassett et al., 2011), emotions (Betzel et al., 2017), and personality traits (Liegeois et al., 2017), to name a few. Moreover, alterations in dynamic resting-state FC have been extensively documented in a growing number of brain disorders including, among others, autism (Harlalka et al., 2019), ADHD (Lacy and Calhoun, 2018), depression (Kaiser et al., 2016), schizophrenia (Rashid et al., 2014), Parkinson's disease (Engels et al., 2018), and substance use disorders (Vergara et al., 2017). Yet, most, if not all, studies on dynamic FC have either entirely overlooked the cerebellum or have poorly represented by it by a few regions-of-interest that do not cover important functional regions of interest.

Considering that the brain is naturally dynamic, continuously integrating information and refining internal representations of the world to anticipate and efficiently execute adaptive behaviors (Lurie et al., 2020), and given the postulated role for the cerebellum in the adaptive control of cognitive processes at different timescales (Xu-Wilson et al., 2009), we hypothesized that the dynamics of cerebrocerebellar FC, during rest, could have a behavioral relevance, possibly capturing aspects of cognition, behavior, and pathophysiology not accounted for by traditional, time-averaged FC. In this thesis, we address this hypothesis in two independent resting-state fMRI studies that lay special emphasis on the dynamics of cerebro-cerebellar FC and their relation to complex behaviors, such as impulsivity, and brain disorders, such as alcohol use disorder.

This Thesis

The thesis is divided into two parts, the first of which includes two independent literature review chapters. In the first chapter, we offer a general overview of the growing field of research into cerebellum's cognitive functions, starting with a historical background that highlights the shift in the understanding of the cerebellum, which coincided with the rise of functional neuroimaging, especially fMRI, as prominent research tools in cognitive and systems neuroscience. We then summarize the functional neuroanatomy of the cerebellum in the light of influential findings from rsfMRI and the theories that define the function and dysfunction of cerebellum, namely the Universal Cerebellar Transform and the Dysmetria of Thought. In the second literature review chapter, we present an extensive overview of fMRI and FC analysis, starting with a historical review of some important checkpoints in the relatively short history of fMRI, highlighting the old-new debates surrounding brain function and how the introduction of fMRI catalyzed successive waves of studies aimed at mapping the brain's functional network organization at different scales of topology, space, and time. Then, we briefly summarize the physical, physiological and data preprocessing basics of fMRI. Finally and foremost, we emphasize on some of the most commonly used methods in the analysis of static and dynamic FC, highlighting the technical details, values, and limitations of each approach.

The second part of the thesis introduces the experimental work carried out in two separate studies to explore the dynamics of cerebro-cerebellar resting-state FC in the light of recent hypotheses and findings implicating the cerebellum in complex behaviors and brain disorders, most notably impulsivity and alcohol use disorder (Chanraud et al., 2011; Chanraud et al., 2013; Jung et al., 2014; Miquel et al., 2019). Importantly, the two studies are presented in the form of articles. In the first study, third chapter overall, we explore a recently advanced hypothesis for a cerebellar role in impulsivity—a complex personality trait mediated by multiple cognitive systems and defined as the tendency to act rashly under the effect of emotions or in response to rewarding cues. Miquel et al. (2019) have recently advanced this hypothesis leaning on scattered but converging evidence from clinical observations and animal models suggesting that cerebellar lesions and cerebrocerebellar dysconnectivity are associated with overt impulsive and compulsive behaviors. In particular, studies have found that disrupting cerebellar function may induce an imbalance between top-down cognitive control and bottom-up reward processes, contributing to rapid decision making and intolerance to delays in reward delivery (Miquel et al., 2019). So far, however, the relation between individual differences in normal trait impulsivity, which might underlie the liability for a broad range of psychopathology, and cerebro-cerebellar functional coupling has not been characterized and remains unclear. Given the influence of multiple brain systems on this complex trait (Davis et al., 2012) and the postulated role for the cerebellum in coordinating diverse streams of information underlying complex cognitive processes (Schmahmann, 2016b), we hypothesized that individual differences in multiple facets of impulsivity could be encoded in broad patterns of information processing involving the cerebellum and emerging from dynamic functional interactions among integrative brain systems at different timescales. To test this hypothesis, we sought to quantify the time-averaged (static) and timevarying (dynamic) FC between the cerebellum and distinct cerebral networks and test for associations with self-reported impulsivity, in a group of healthy young individuals (N=134, ages 20-40). Accordingly, we performed group independent components analysis to delineate separate cerebral and cerebellar RSNs, static FC analysis to estimate time-averaged FC matrices, and hidden Markov models (HMM) to estimate subject-specific FC states defined as replicable patterns of connectivity that transiently recur over time (Vidaurre, Smith, and Woolrich, 2017; Vidaurre et al., 2018). This methodology enabled us to explicitly model the temporal dynamics of cerebro-cerebellar connectivity with enhanced representation of the cerebellum and, subsequently, estimate summary measures of the overall strength and temporal variability of resting-state FC between the cerebellum and distinct large-scale brain systems.

In the second study, fourth chapter overall, we explored the differences in the dynamics of cerebro-cerebellar resting-state FC between a group of participants diagnosed with alcohol use disorder (AUD; N=18) and a group of unaffected controls (N=18). AUD is a chronic and relapsing brain disorder, characterized by systems-level alterations underlying a broad range of cognitive deficits, most notably in executive function, caused by prolonged and excessive intake of alcohol (Sullivan, Harris, and Pfefferbaum, 2010). One of the severely altered brain systems in AUD is the cerebro-cerebellar system, and more precisely, the frontocerebellar networks
that play an important role in a diversity of executive functions (Sullivan and Pfefferbaum, 2005). Previous studies have revealed that frontocerebellar resting-state FC is severely altered in AUD, associating it with deficits in cognitive functions such as working memory and impulse control (Chanraud et al., 2011; Chanraud et al., 2013; Jung et al., 2014). However, these findings have been based on timeaveraged measures of FC, which are blind to potentially adverse effects inflicted by alcohol intake on cognitive processes that necessitate a dynamic integration of multiple brain systems at short timescales, such as adaptive cognitive control and working memory (Chanraud et al., 2013; Douw et al., 2016). Therefore, we hypothesized that the dynamics of cerebro-cerebellar FC, during rest, would differ between AUD subjects and controls, especially in the frontocerebellar executive control circuit. To test this hypothesis, we adopted a sliding window correlation method (Hindriks et al., 2016) to divide BOLD timeseries, extracted from finely parcellated cerebral and cerebellar regions (Power et al., 2011; Seitzman et al., 2020), into overlapping segments and measure FC within each segment, which permitted modelling fast variations in cerebro-cerebellar FC patterns across short time intervals. Then, we assessed group differences in terms of temporal variability of FC patterns between the cerebellum and large-scale cognitive networks—the default mode, executive control, attention, and salience networks. Moreover, we performed multilayer community detection analysis-a powerful extension of traditional graph theory community detection methods—which permitted the quantification of short-term changes in the brain's modular structure using measures of flexibility and integration computed in the cerebellum as well as large-scale cognitive networks (Braun et al., 2015; Gifford et al., 2020; Mucha et al., 2010). Finally, the thesis closes with a general conclusion chapter that summarizes the findings, answers the main hypothesis, and presents suggestions for future research.

Part I

Literature Review

Chapter 1

The Cerebellum in Cognition: A General Overview

Abstract

The cerebellum or the "little brain" has intrigued researchers and clinicians interested in the brain since the time of antiquity. The principle anatomic and cytoarchitectonic features of the cerebellum were recognized and characterized early, and the strong emphasis on its role in coordinating movements has been around since the late 18th century. However, over the last three decades, accumulating evidence has indicated that the cerebellum is involved in diverse functions that transcends the sphere of the sensorimotor domain. This view has emerged from studies of viral tract tracing in animals, functional neuroanatomy, functional neuroimaging, neuropsychology, and brain stimulation, with findings implicating the cerebellum in domains as diverse as cognitive control, working memory, attention, language, and social cognition. Moreover, sophisticated models of how the cerebellum helps refine movements through implementations of forward models and error-based learning have provided some evidence of the core mechanisms behind cerebellar functioning in the cognitive and affective domains. This has been supported by evidence of an essentially uniform cerebellar anatomy, functionally diverse cerebro-cerebellar connections, and cognitive and affective dysregulations that arise from cerebellar injuries or brain disorders. Importantly, task-based and resting-state functional magnetic resonance imaging (rsfMRI) techniques have provided unprecedented non-invasive support for the involvement of the cerebellum in a broad range of motor and cognitive functions, revolutionizing the ways the neuroscience community explore the functions and dysfunctions of the little brain. In light of these advances, this chapter presents a summary of the growing field of research into the functions of the cerebellum. It starts with a brief historical background, then moves on to describe the functional neuroanatomy of the cerebellum and the theories of cerebellar functions and dysfunctions.

1 A History of Cerebellar Function: Not So Little After All

Notions regarding the function of the cerebellum has been around since times of antiquity and have included the belief that it provides strength for motor nerves, is an epicenter of memories and dreams, it controls sensory functions, is involved with involuntary actions such heart beat and respiration, and is the seat of emotions and love (see Schmahmann, 2016a for a comprehensive review). In modern times, it seems that these historical accounts, although not based on solid evidence nor a rigorous scientific methodology, are not very far from reality. Contemporary accounts have found that the cerebellum, in fact, contributes to motor coordination and learning (De Zeeuw and Ten Brinke, 2015), working memory (Deverett et al., 2019), episodic memory (Fliessbach et al., 2007), autonomic functions (Wu et al., 2014), and emotion regulation (Adamaszek et al., 2017).

1.1 The Cerebellum in Sensorimotor Control and Learning

Traditionally, the cerebellum has been thought of as a mere sensorimotor structure. The cerebellar contribution to sensorimotor functions has two broad aspects (Manto et al., 2012). The first, which is known as motor **control and coordination**, refers to the moment to moment gathering of external sensory information with a "motor command" from the primary motor cortices to produce an accurate movement at an appropriate speed and timing. The interest in the cerebellar role in sensorimotor control and coordination arose early in the late 18th to early 19th centuries following careful observations in animal models of the consequences of cerebellar ablation and damage (Buckner, 2013). In particular, Marie-Jean-Pierre Flourens (1824) was the first to show that the cerebellum is responsible for the coordination, rather than generation, of voluntary movement and gait in pigeons. Flourens wrote "all movements persist following ablation of the cerebellum: all that is missing is that they are not regular and coordinated" (Flourens, 1842). Around the same period, François Magendie's studies of cerebellar lesions provided evidence that the cerebellum is essential for maintaining posture and equilibrium. Disturbances of motor control

and coordination following a focal cerebellar lesion in monkeys were demonstrated by several neuroscientists in the late nineteenth century, most notably Luigi Luciani who described thee basic symptoms of cerebellar lesions: asthenia (i.e., muscular weakness), atonia (i.e., muscular slackness), and astasia (i.e., posture and equilibrium deficits; Luciani, 1891). Later, in the 1930s, it was established that the cerebellum is fundamental for adjusting the timing and speed of movement initiation, which ensures that movements are appropriately selected and sequenced at a fine level (Holmes, 1939). The term motor ataxia was later introduced to describe an array of motor syndromes caused by damage to the cerebellum and broadly characterized by lack of temporal coordination between movements, among other symptoms (Schmahmann, 2000). For a detailed review of cerebellar functioning in motor control, see (Manto et al., 2012).

The second aspect of the cerebellar contribution to sensorimotor function is motor learning, which is the plastic consequence of motor control (Manto et al., 2012). Motor learning, sometimes referred to as *motor plasticity*, refers to a longterm change of the "procedural memory" in the relation between an input signal and a resulting motor output induced by continuous practice or repetition (Marr and Thach, 1991; Sokolov, Miall, and Ivry, 2017; Thach, 1996). Studies from the early to mid twentieth century have provided evidence that the cerebellum, besides the "online" coordination of ongoing movements, is important for long-term motor learning, acquisition of new skills and formation of habits (Miquel et al., 2019). The theories of cerebellar motor learning has been largely motivated by the seminal works of David Marr, Masao Ito, and James Albus who, in the mid 20th century, proposed computational and mathematical models of cerebellar functions, especially in sensorimotor learning, based on the neurocircuitry and cellular architecture of the cerebellum (Albus, 1971; Marr and Thach, 1991; Marr and Thach, 1991). Within these models, the cerebellum forms an internal representation of the environment through repeated performance and feedback mechanisms. As a movement is practiced, the cerebellum allows it to be executed automatically without dynamic feedback from the environment. In simpler terms, the cerebellum predicts the outcome of a movement and then adaptively fine-tunes cortical motor commands, in case of a mismatch between prediction and the actual outcome, to adjust the movements

in the next iterations, accordingly. Then upon a series of repetitions through a trialand-error or **error based learning** process, movements become automated, requiring less allocation of neural resources (Knierim, 1997). Recently, analogous computational principles of the cerebellum have been proposed to support an automated and coordinated execution of higher-order cognition (Buckner, 2013; Schmahmann et al., 2019). For a recent review of the different models of cerebellar sensorimotor learning, see Kawato et al. (2020).

1.2 The Cerebellum and Cognition

For a long period of time, the emphasis of the literature on the cerebellum was solely focused on sensorimotor control and learning (Strick, Dum, and Fiez, 2009). This was partly driven by a peculiar feature of the cerebro-cerebellar circuitry that has precluded traditional anatomical techniques from delineating the cerebellum's full functional properties. In general, two main reason contributed to the entrenched view of sensorimotor function: the obviously severe motor disturbances induced by cerebellar lesions and the absence of monosynaptic connections between the cerebellum and the cerebrum, which precluded investigations into the organization of the cerebellum using conventional anterograde and retrograde viral tracing techniques that do not cross the synapse (Buckner, 2013). However, a shift in the understanding of the cerebellum has taken place over the past 30 years. In an incisive review in the mid-1980s by Henrietta Leiner, Alan Leiner, and Robert Dow, a summary of evidence based on observations of cerebellar evolution in mammals (including humans) introduced one of the early hypotheses that the cerebellum is involved in cognitive functions beyond the sensorimotor domain (Leiner, Leiner, and Dow, 1986). Their hypothesis was based on cross-species observations that the posterior cerebellum and the dentate nucleus (a cluster of neurons embedded in the white matter of the cerebellum) are significantly enlarged in humans, and that this enlargement mirrors that of the prefrontal cortex. Based on this observation the authors hypothesized, "The phylogenetically newest structures of the cerebellum may contribute to mental skills in much the same way that the phylogenetically older structures contribute to motor skills". In the late 1980s to early 1990s and on, researchers conducting trans-synaptic viral tracing studies, careful clinical observations in patients with cerebellar damage, and importantly, functional neuroimaging experiments, have been able to finally confirm this hypothesis based on numerous evidence.

Direct evidence for a cerebellar role in cognition have surfaced from studies of anatomical cerebro-cerebellar circuits using novel transneuronal or trans-synaptic tract tracing techniques (Middleton and Strick, 1994). Trans-synaptic viral tracing uses viruses that spread across synapses that enable the mapping of polysynaptic circuits, such as those between the cerebrum and the cerebellum, thereby overcoming the limitations of traditional tracing techniques. In one the early influential studies, Middleton and Strick (1994) used trans-synaptic viral tracers on nonhuman primates to examine whether parts of the cerebellar cortex that receive projections from the primary motor cortex and prefrontal cortex (area 46). Their findings showed that afferents from the primary motor cortex (M1) terminated mainly in the anterior cerebellum (primary motor map; lobules IV,V,VI) and in a small portion in the posterior cerebellar (secondary motor map; lobules VIIB and VIII). Interestingly, they found that afferents from the prefrontal area 46 (i.e., dorsolateral prefrontal cortex) terminated in large region in the posterior cerebellum (Crus I and Crus II) that is totally segregated from the primary motor cortex and motor regions of the cerebellum. Thus, these observations suggested that multiple closed-loop circuits represent the fundamental architectural feature of cerebro-cerebellar interactions (Kelly and Strick, 2003). Later tract tracing studies revealed large swathes of cerebellar projections to higher-order cortical association regions, notably the posterior parietal and cingulate cortices, as well as subcortical structures such as the basal ganglia, amygdala, and thalamus (see (Bostan and Strick, 2013) for a comprehensive review on the topic). Interestingly, very recent studies have also shown that the cerebellum directly projects to the sub-thalamic nuclei, nucleus accumbens, and most importantly, the ventral tegmental area, the center of dopimanergic cell bodies, ascribing the cerebellum a pivotal role in the reward system (Carta et al., 2019). Collectively, trans-synaptic viral tracing results have revealed that extensive cerebellar association regions fall in between the primary and secondary motor maps, providing the first clue of a parsimonious organizational principle of the cerebellar



FIGURE 1.1: (A) The cerebellum is connected to the cerebral cortex through poly-synaptic connections: input projections from the cerebral cortex first synapse on the ipsilateral pons and then cross to the contralateral cerebellar cortex. Output projections first synapse on the dentate then cross to synapse in the contralateral thalamus and finally project to the cerebral cortex. (B) Neurons in the cerebellum labelled by injecting trans-synaptic viruses in the prefrontal are 46. The viruses can cross the synapses in the pons and pass to the green region, suggesting it connects to the prefrontal cortex. The topography of the projections is specific and distinct from the motor zones. Figures adapted from Buckner, 2013 and Bostan and Strick, 2013, with permissions.

cortex, which putatively allows the cerebellum to communicate with brain regions of specialized primary functions to regions at the higher levels of integrative cognition and emotion processing (Bostan and Strick, 2013).

Along a parallel research lane at the time, observations of cognitive and affective impairments in patients with cerebellar abnormalities in the posterior cerebellum surfaced (Fiez et al., 1992; Grafman et al., 1992; Schmahmann, 1991b; Schmahmann and Sherman, 1997). Of particular importance are the observations made by Jeremy Schmahmann in the 1980s and 1990s, which culminated in the emergence of three important concepts: the *Cerebellar Cognitive Affective Syndrome* (CCAS), the *Dysmetria of Thought Theory*, and the *Universal Cerebellar Transform* (Schmahmann, 2019). In particular, the CCAS describes an array of symptoms or deficits in executive function, linguistic processing, spatial cognition, and affective dysregulations ranging

from emotional distress, depression, to impulsiveness, disinhibition and psychotic features observed separately or collectively in patients suffering from cerebellar atrophies caused by strokes (Schmahmann and Sherman, 1997). In particular, it arises from damage to the cognitive cerebellum in the posterior cerebellar lobe, and is postulated to reflect a cognitive dysmetria analogous to ataxia in sensorimotor control (impaired balance, gait, and limbs and eye movements) observed in patients with damage to the sensorimotor cerebellum (Hoche et al., 2018). The umbrella term used to describe the motor and cognitive deficits arising from cerebellar damage is the "Dysmetria of Thought Theory", predicated on the so called Universal Cerebellar Transform, or UCT (Guell, Gabrieli, and Schmahmann, 2018a; Schmahmann, 2019). The theory of the UCT posits that the computational process underlying cerebellar role in modulating movement, cognition and emotion are unitary, building on the striking uniformity of cerebellar anatomy (Schmahmann et al., 2019). That is, the cerebellum is believed to serve a domain-general function, while having diverse heterogeneous connections to motor and non-motor structures. Thus, the Dysmetria of Thought theory posits that the motor ataxia and CCAS are consequences of a unitary neurological dysfunction, known as the Universal Cerebellar Impairment (Schmahmann, 2004).

These collective observations provide evidence of anatomical and pathological substrates for contributions of the cerebellum to cognition. However, the major breakthroughs and direct empirical evidence on the participation of the cerebellum in cognitive and affective functions have come from functional neuroimaging studies Buckner, 2013. With the introduction of functional neuroimaging to neuroscience in the 1980s, Petersen et al. (1988) published a seminal paper with extraordinary findings on the functional anatomy of single-word processing using positron emission tomography (PET). Unintentionally, they found that when participants generated words, a recurrent response (i.e., activity) occurs in the right posterolateral cerebellum in language production. Based on this finding, Fiez et al. (1992) conducted a single-subject PET study on a patient with cerebellar lesion to the right posterolateral cerebellum. Interestingly, they found that the patient performed normally on standard language tasks, but had profound deficits in practice-related

learning and detection of errors tasks; two important functions of the cerebellum in motor control and learning. These seminal results suggested that some functions performed by the cerebellum may be generalized beyond a purely motor domain. Anchoring from these initial observation, later experiments using functional magnetic resonance imaging (fMRI; Ogawa et al., 1990), in the early 1990s, have detected posterior cerebellar activation during non-motor learning and cognitive processing tasks (Desmond, Gabrieli, and Glover, 1998). Task-activation associations are based on the concept of blood-oxygen-level dependent (BOLD) signals that index changes in brain metabolism in a given brain region (Ogawa et al., 1990), which in turn is considered a proxy to neuronal activity in response to task demands (Glover, 2011). The exponential growth and success of task-activation experiments, owing to the non-invasive and non-ionizing use of fMRI, catalyzed many studies that detected large number of activations in the posterior cerebellum across a wide range of cognitive tasks (Figure 1.1), including executive function, language, working memory, emotional processing, spatial attention, and social cognition, leaving little doubt that the origins of these responses are non-motor and the cerebellum is indeed involved in higher-order cognitive functions (for recent reviews of studies of taskactivation in the cerebellum, see Keren-Happuch et al., 2014; Stoodley, Valera, and Schmahmann, 2012).

In a recent large-scale task-based fMRI study, King et al. (2019) have been able to extensively map the functional sub-regions of the whole cerebellum using a rich battery of tasks performed in hours-long fMRI experiments designed to tap into a broad range of cognitive processes (King et al., 2019). Shortly before that, however, a surprisingly powerful fMRI approach, that does not include eternally cued tasks, have been used to comprehensively map the organization of the human cerebellar cortex (Buckner et al., 2011). The approach has been motivated by the observation that the functional organization of the brain can be inferred by measuring the level of synchrony between spontaneous low-frequency fluctuations in intrinsic activity between brain regions, when individuals rested in a state of mind wandering (Biswal et al., 1995; Fox and Raichle, 2007; Van Den Heuvel and Pol, 2010).



FIGURE 1.2: Activations in the cerebellum in response to different tasks in meta-analysis (left), a single-subject case study (middle), and group analysis right). Figure reproduced from Stoodley and Schmahmann (2009), with permission.

BOLD signals extracted from regions that have monosynaptic or polysynaptic connections tend to fluctuate together, during rest, and hence exhibit functional connectivity (FC), even in the absence of task (Biswal et al., 1995; Buckner et al., 2011). In this context, studies using resting-state FC analysis have been able to delineate functional regions in the cerebellum that intrinsically connect to large-scale cerebral functional networks previously identified across a multitude of studies (Calhoun, Kiehl, and Pearlson, 2008; Damoiseaux et al., 2006; Power et al., 2011; Rosazza and Minati, 2011; Smith et al., 2009; Yeo et al., 2011).

Two resting-state fMRI (rsfMRI) studies carried in parallel by Habas et al. (2009) and Krienen and Buckner (2009) have mapped the functional topography of the cerebellum based on functional correlations with different regions in the cerebral cortex. Although the studies have relied on two different techniques to quantify

and analyze cerebro-cerebellar FC, their findings have converged on qualitatively overlapping findings. On one hand, Habas et al. (2009) used a technique that decomposes high-dimensional data to a set of spatial maps representing networks of highly interconnected regions, often called resting-state networks (RSNs). They delineated spatial maps showing that regions from the posterior cerebellum connect to executive control, salience network, and default mode networks that are involved in higher-order cognition. Importantly, little to no overlap was detected between these cerebellar regions and the sensorimotor anterior cerebellum that mostly connected to the primary motor cortices. These results suggest that the posterior cerebellum makes contributions executive control, salience detection, and episodic memory/self-reflection. On the other hand, Krienen and Buckner (2009) used a seed based analysis, which entails selecting a region of interest in the prefrontal cortex and estimating its FC with the whole cerebellum to see to which regions it mostly connects. They found contralateral and segregated representations of at least four different prefrontal regions in the cerebellum, suggesting that frontocerebellar functional connections during rest reflect the closed-loop circuitry previously identified using tract tracing, wherein different prefrontal areas receive input from the very same cerebellar regions that they project. Together, these studies provided groundbreaking evidence that the cerebellum functionally interacts with higherorder cognitive networks. In a later study, Buckner et al. (2011) used rsfMRI data to map, for the first time, the entire cerebellum based on the FC between each point (i.e., voxel) in the cerebellum and a previously created 7-Network and 17-Networks maps of the cerebral cortex (Yeo et al., 2011). This yielded a 7-Network (Figure 1.4) and a 17-Network representations of well-known cerebral networks in the brain. Importantly, the majority of the human cerebellum falling between the anterior and posterior motor representations was found to map to cerebral cognitive and affective networks, mirroring the cerebral asymmetries for language and attention (Buckner, 2013).

Finally, studies of brain disorders using task and resting-state fMRI have revealed alterations in cerebro-cerebellar FC, contributing to a wide array of symptoms ranging from motor disturbances to cognitive and affective deficits. In this context, many studies have implicated the cerebellum, along with the prefrontal



FIGURE 1.3: A complete map of the cerebellum to a mutli-domain task battery. The cerebellum can be involved in functions ranging from motor planning (top-right) to autobiographical memory (bottom-right). Figure reproduced from King et al. (2019), with permission.

cortex and basal ganglia, in brain disorders, such a substance addiction (Chanraud et al., 2013), schizophrenia (Zhuo et al., 2018), autism (Khan et al., 2015), and attention deficit/hyperactivity disorder (ADHD; Stoodley, 2016), contributing to a broad range of executive and affective deficits that manifest in symptoms such as behavioral disinhibition, hyperactivity, craving, compulsive and impulsive behaviors, poor performance on cognitive tasks, personality changes, and emotional distress (Schmahmann et al., 2019). Owing to the advent of fMRI, these findings, among others from task-activation experiments (King et al., 2019; Stoodley, Valera, and Schmahmann, 2012), have placed the cerebellum on the neurobiological map of a wide variety of cognitive abilities and brain disorders that feature cognitive deficits, making it an important cognitive structure and a potential therapeutic target that should not be excluded from anatomical and functional models of complex human behaviors and brain disorders. Based on the abovementioned historical observations and recent findings, it seems that the "little brain" is simply too large to ignore in the functional and anatomical models of cognition, emotions, and brain disorders and is not so little after all. For a key consensus review on the role of the



FIGURE 1.4: Resting-state functional connectivity studies have shown that each cerebellar region can be linked to a region in the cerebral cortex (A–D). (A-B) the 7-Network functional maps of the cerebral cortex.
(C-D) the 17-Network functional maps of the cerebral cortex.
(E) The 17-Network functional map in the cerebellum. Figure reproduced, with permission, from Sokolov, Miall, and Ivry (2017), originally adapted from Buckner et al., 2011 and Yeo et al. (2011).

cerebellum in motor function and cognition, see (Koziol et al., 2014).

2 Gross Anatomy of the Human Cerebellum



Cerebellar cortex

FIGURE 1.5: Gross Anatomy of the Cerebellum. On the rostral-caudal directions, the cerebellum is divided into two large lobes along with a smaller third lobe: The anterior sensorimotor lobe, the posterior cognitive lobe, and the smaller floccunolodular lobe involved in vestibular functions. The two main lobes are separated by the primary fissure. On the transversal direction, the cerebellum is made up of two large lateral hemispheres, connected to the contralateral hemispheres in the cerebral cortex, separated by a thin intermediary zone called the vermis that is mainly involved in limbic functions. Figure adapted from Neuroscience Online.

The cerebellum is located at the base of the brain in the "hindbrain" region, with the cerebral cortex above it and the brain stem in front of it. The cerebellum is separated from the cerebrum by a layer of tough *dura mater*. The human cerebellum consists of three lobes and two hemispheres connected by a narrow midline structure, called the vermis (Figure 1.5). The hemispheres and the vermis are each divided into 10 lobules, with the primary fissure defining the border between the anterior "sensorimotor" and posterior "cognitive" lobes. Similarly to the cerebral cortex, the cerebellum has an outer cortical layer made up of a very tightly folded layer of gray matter (GM): the cerebellar cortex. The cerebellar cortex has a highly conserved "crystal like" structure laid out with a highly stereotyped geometry (i.e., accordion-like ridges) and consisting of three layers: Molecular layer, Purkinje cell layer, and Granule cell layer each having different cytoarchitectonic features. Each ridge of the cerebellar cortex is called a folium (Figure 1.5; top left). It is estimated that, if the human cerebellar cortex is unfolded, it would span about 1 meter long and 5 centimeters wide. Beneath the GM there is an inner layer of white matter (WM) that contains small but dense clusters of GM called the deep cerebellar nuclei; the main output of the cerebellum to other brain regions. The input to the cerebellum comes from the pontine nuclei in the pons; the pontine nuclei receive extensive projections from the cerebral cortical and sub-cortical regions and then relays the information to the cerebellar cortex or directly to the deep cerebellar nuclei. The cerebellar cortex (the Purkinje cell layer) processes the input information and also relays them to deep cerebellar nuclei in the form of inhibitory synapses. Finally, the deep cerebellar nuclei, especially the dentate nucleus, send efferent signals to the cerebral cortex and subcortex via direct connections with the thalamus. This polysynaptic network has been the major contributor to the ambiguity surrounding the organization and functions of the cerebellum, mainly because conventional anterograde and retrograde tracing techniques do not cross poly-synapses. For a detailed description of the cerebellum's gross anatomy, the reader is referred to the textbooks and reviews on the subject, such as (Schmahmann et al., 2000; Voogd and Glickstein, 1998).

3 Functional Organization of the Human Cerebellum

In recent years, there has been an great effort to map the complete functional organization of the human cerebellum using fMRI. Early task-based fMRI studies have provided traction and a general sense for how the cerebellum might be functionally organized, but they have only revealed discrete maps of few active regions in response to an externally-cued stimuli (Stoodley, Valera, and Schmahmann, 2012). Recently, however, there has been a major effort by King et al. (2019) to make a functional map of the entire cerebellar cortex using a large multi-domain battery



FIGURE 1.6: Buckner's 7-Networks cerebellar map (left) based on a "winner-takes-all" strategy that assigns each voxel in the cerebellum to a cerebral cortex network (right) based on maximum functional connectivity. Figure adapted from Buckner et al., 2011, with permission.

of 47 tasks and long hours of task fMRI scans. Findings from this study have uncovered a detailed map of ten cerebellar functional zones related to tasks of language, working memory, motor planning, emotion processing, and autobiographical memory, among others (Figure ??. As expected by the authors, strict anatomical lobular boundaries, commonly used to describe different functional zones in the cerebellum, did not perfectly coincide with the functional subdivisions, suggesting that lobular representations of the cerebellum are not suitable to explore its function. Shortly before that, however, parsimonious functional organization maps in the cerebellum have come from task-free, or rsfMRI studies (Allen et al., 2005; Buckner et al., 2011; Habas et al., 2009; Strick, Dum, and Fiez, 2009). These studies have been motivated by preceding similar studies that focused on delineating the complete functional organization of human cerebral cortex by analyzing the



FIGURE 1.7: Mapping of cerebellar functional networks to anatomical boundaries. DMN=Default Mode Network, FPN=Fronto-Parietal Network, PFC: Prefrontal Cortex. Figure adapted from Bernard and Mittal (2014), with permission.

resting-state FC patterns between brain regions in large datasets using data-driven techniques (Buckner et al., 2011). Of particular importance, is the study by Buckner et al. (2011) who used a "winner-takes-all" strategy that assigns each cerebellar region to the cerebral cortical network (Power et al., 2011; Yeo et al., 2011) with the most similar profile of connectivity, in a large group of healthy subjects (N=1000). This yielded a 7-Network map (Figure 1.6) of major cerebellar networks as well as a 17-network map, mirroring the 7 and 17-Network maps (Figure 1.4) previously delineated in the cerebral cortex (Yeo et al., 2011). These cerebellar functional maps included representations of most well-known cerebral resting-state networks, with findings showing that the majority of the cerebellum maps onto higher-order cognitive networks (Buckner, 2013).

On the group level, cerebellar functional networks are dominated by common organizational principles (Marek et al., 2018). That is, sensorimotor networks are contralaterally represented in two maps: the primary representation in the anterior cerebellum (overlapping with lobules I-IV and V and extending into lobule VI) and a smaller secondary representation (lobule VIII) in the posterior cerebellum, whereas the cognitive networks are represented in three maps (overlapping with lobules IV/V/VI/Crus I, lobules Crus II/VIIB/VIII and lobules IX/X) situated in

the posterior and lateral cerebellar regions in between the primary and secondary motor maps (see Figures 1.6 and 1.7; and Bernard et al., 2012; Guell, Gabrieli, and Schmahmann, 2018b for reviews). Yet, on the individual subject level the cortical network representations are highly subject-specific in terms of distribution, size, and location, especially within the cognitive cerebellum (Marek et al., 2018). Using the highly-sampled Midnight Scan Club (MSC) dataset (10 subjects, 10 sessions), Marek et al. (2018) found that the cerebellum contains reliable, individual-specific network organization that varies significantly when compared to the cerebral cortex. Moreover, across all individuals, the frontoparietal network, thought to support adaptive control, was the only network to be over-represented in the cerebellum compared to the cerebral cortex.

Recently, there has been a focus on deriving functional connectivity "gradients" using a a nonlinear dimensionality reduction technique and can be used to analyze similarities between FC profiles across the brain, known as diffusion embedding (Coifman et al., 2005). Margulies et al. (2016) used diffusion embedding to provide a simple and powerful description of a principal gradient of resting-state FC in the cerebral cortex. This study revealed representational gradient-like hierarchies of information processing ranging from specialized unimodal motor regions to integrative transmodal regions (DMN), confirming a hypothesized primary-unimodaltransmodal hierarchical principle of the cerebral cortex (Mesulam, 1998). Inspired by these findings, Guell et al. (2018) used diffusion embedding to compute FC gradients within the cerebellum (Figure 1.8). Comparing their results with the whole-cerebellum map obtained by Buckner et al. (2011) and task activation maps, the authors have shown, for the first time, that the cerebellum follows a gradual "gradient-like" organization which progresses from primary (motor) to transmodal (DMN) regions, mirroring that of the cerebral cortex. Also, a secondary axis was revealed that extends from DMN to executive control processing. Further, these two principal gradients revealed the general organizational principal of the cerebellum that defines the relationship between the double motor representation (lobules I-VI and VIII), and a triple nonmotor/cognitive representation (lobules VI/Crus I, Crus II/VIIB, IX/X) defined in earlier study by the same authors \citet {guell2018triple}.

For other prominent works on the functional network organization of the cerebellum, see these key papers Allen et al., 2005; Buckner et al., 2011; Habas et al., 2009; Guell et al., 2018; King et al., 2019; Krienen and Buckner, 2009; Marek et al., 2018; O'reilly et al., 2010; Strick, Dum, and Fiez, 2009.

4 Theories of Cerebellar Function and Dysfunction

4.1 Universal Cerebellar Transform

The cerebellar cortical architecture is essentially invariant throughout (contrasting with the heterogeneous cerebral cytoarchitecture), which has given rise to the idea that the cerebellum performs a domain-general function across sensorimotor and cognitive processes, a principle expressed in the notion of the **universal cerebellar** transform (UCT) (Schmahmann, 2000). Superimposed upon the UCT principle is the presence of highly organized and functionally diverse cerebellar connections with the cerebral cortex, sub-cortex, brain stem, and spinal cord, enabling the cerebellum to modulate diverse streams of information that originate in unimodal and multimodal brain systems, in a concise and contextual manner (Guell, Gabrieli, and Schmahmann, 2018c). This functional diversity might not be compatible with the UCT, but cerebellar regions are thought to differ in the projections of their inputs and outputs to different brain regions, while performing similar computations (Voogd and Glickstein, 1998; Schmahmann, 2016b). The cerebellum thus supports an "embodiment" of cognition, which involves a constitutive dependence between sensorimotor, cognitive, and affective functions, by integrating multiple internal representations with external stimuli and self-generated responses and, ultimately optimizing performance (Guell, Gabrieli, and Schmahmann, 2018a). This universal integrative principle of cerebellar functioning maintains movement, cognition, and behavior fine-tuned around a homeostatic baseline (Diedrichsen et al., 2019; Schmahmann, 2016b; Schmahmann, 2019; Sokolov, Miall, and Ivry, 2017).



FIGURE 1.8: Cerebellar functional connectivity gradients and their relationship with task activity maps (from Guell, Gabrieli, and Schmahmann, 2018b) and resting-state maps (from Buckner et al., 2011). Gradient 1 extended from motor regions to language/DMN regions. Gradient 2 extends from DMN regions to executive control regions. (A) Cerebellum flatmap of gradients 1, gradient 2, and a lobular atlas of the cerebellum. (B) Scatter plot of the first two gradients. Each dot corresponds to a cerebellar voxel, position of each dot along x and y axis corresponds to position along Gradient 1 and Gradient 2 for that cerebellar voxel, and color of the dot corresponds to task activity (top) or resting-state network (bottom) associated with that particular voxel.

Figure reproduced from Guell et al. (2018), with permission.

4.2 The Dysmetria of Thought Theory

Besides the recent characterizations of cerebellar cytoarchitecture and functional organization, the theories of UCT and embodied cerebellar cognition have been supported by recurring observations of common patterns of deficits across sensorimotor and cognitive domains caused by cerebellar injury or brain disorders, notably addiction (Schmahmann, 1998; Sullivan and Pfefferbaum, 2005). Based on these observations and given that the UCT is the essential functional/computational contribution that the cerebellum offers to distributed neural systems, then, by deduction, there should be universal cerebellar impairments that manifest uniformly across disparate functions (Schmahmann et al., 2019). In this context, many studies have converged on consistent findings that while brain cortical damage may result in a total loss of a certain function, cerebellar damage degrades the precision, timing, and efficiency of that function as observed in patients with linguistic deficits, executive deficits as well as motor dis-coordination or ataxia (Guell et al., 2018). These universal cerebellar impairments are collectively defined within the "Dysmetria of Thought" theory (Guell, Hoche, and Schmahmann, 2015). In this sense, when the dystmetria of thought involves the motor domain, the various manifestations of ataxia are evident in loss of coordination in limb movements, eye movements, gait, and speech. However, when the dysmetria involves non-motor, cognitive functions subserved by the posterior cerebellum, it results in cognitive dysmetria, and manifests as the various components of the cerebellar cognitive affective syndrome, or CCAS. Patients with cognitive/affective cerebellar dysfunction may struggle with depressive symptoms and other forms of emotional distress, reflecting dis-coordinated emotions, in addition to impairments in cognitive flexibility, decision making, and attention, which manifest as impulsive and compulsive symptoms as well as impaired ability to multitask automatically (Schmahmann and Sherman, 1997). For more comprehensive reviews on dysmetria of thought, see Guell, Gabrieli, and Schmahmann (2018a), Schmahmann (2004), and Schmahmann et al. (2019).

5 Summary

In this introductory literature review chapter, we reviewed some of the main findings that have ascribed the cerebellum an important role in the cognitive domains. First, we have summarized the progression of cerebellar neuroscience research from the traditional purely motor models to the complex cognitive models, which has been largely facilitated by the introduction of novel methods to viral tract tracing, careful observations of cognitive deficits in patients with cerebellar damage, and, most importantly, the rise of functional neuroimaging to prominence in neuroscience, most notably fMRI. Then, we briefly revisited the gross anatomy of the cerebellum and laid special emphasis on its functional network organization that has been mapped entirely using different analysis techniques across task-based and resting-state fMRI datasets. Finally, we have reviewed the most prominent theories of cerebellar function and dysfunction, namely the *Universal Cerebellar Transform* and *Dysmetria of thought*.

Chapter 2

Functional Magnetic Resonance Imaging and Functional Connectivity Analysis: A General Overview

Abstract

Functional neuroimaging encompasses a wide variety of modalities that can be used to explore brain function and relate a change in brain activity or connectivity with behavior, cognition, and psychopathology. Some modalities directly record neuronal activity as electrophysiological signals or magnetic fields, while other modalities measure changes in glucose or blood oxygen consumption as surrogates of neuronal activity. Of all the functional neuroimaging techniques, functional magnetic resonance imaging (fMRI) has been the most influential in transforming and revolutionizing neuroscience in a relatively short period of time. Since the early 1990s, fMRI has offered various advances over other modalities, such as the non-invasive and non-ionizing use, enhanced spatial resolution, and the ability to explore all brain regions, not just those close to the surface. These features have enabled modern day neuroscientists to explore and infer brain-behavior relationships, non-invasively, in vivo, by measuring localized brain activity in response to task demands, evaluating functional connectivity (FC) patterns during resting-state and task, and correlating these with cognition, behavior, and pathophysiology. This general overview chapter summarizes some important checkpoints in the relatively short history of fMRI, highlighting the early debates surrounding the nature of brain function and how the introduction of fMRI catalyzed successive waves of efforts to map the human brain at multiple scales of space, time, and topology. Then, the chapter summarizes the bases of fMRI, the preprocessing steps necessary to remove background noise, and some of most commonly used methods used in the analysis of FC. Last and foremost, considering that the brain is a dynamic interconnected system, this chapter highlights the shortcomings of traditional time-averaged FC analysis and summarizes some of the approaches tailored for analyzing time-varying FC beyond simple scan-length averages.

1 Functional MRI and Neuroscience: A Brief History

Since its introduction to the clinical and research practices in the early 1980s, magnetic resonance imaging (MRI) has radically transformed the way we look at and explore the human and animal body. With MRI, the ability to diagnose conditions, plan treatments and assess the effectiveness of previous treatments has been greatly enhanced. In fact, MRI is considered a medical marvel with an unparalleled, non-invasive and non-ionizing use and an unprecedented spatial resolution not offered by other imaging modalities. Over the years, MRI has advanced into a brain imaging (or neuroimaging) modality that continues to provide us with new insights into the morphology and pathomorphology of the brain. However, major breakthroughs in fundamental brain research have been made in the past two decades owing to the development of **functional magnetic resonance imaging** (fMRI), informing us of the function and dysfunction of brain at different timescales and across different populations. Informed by fMRI, sophisticated models of brain function, structure, and physiology are constantly evolving and enhancing our understanding of the human and animal brain.

1.1 Early Beginnings: Functional Localization

Over the past few decades, the scope of neuroscience has expanded enormously to include a multitude of functional neuroimaging modalities that enable exploring the brain at multiple spatiotemporal scales, from individual neurons to large-scale brain systems and on timescales extending from milliseconds to hours (Figure 2.1). However, much of the growth of today's neuroscience, and more specifically cognitive neuroscience, in terms of prevalence, impact, and scope is attributed to the advent of MRI-based technologies, especially fMRI (Poldrack, 2008).

Functional MRI emerged in the early 1990s (Kwong et al., 1992; Ogawa et al., 1990) as a non-invasive, *in vivo* and easy-to-use MRI-based technique to explore brain function rather than anatomy at a relatively enhanced spatial resolution compared with other modalities at the time (Figure 2.1). In a relatively short period of



FIGURE 2.1: The spatial and temporal resolutions of the mostly used modalities that measure brain activity, as available in 2014 (large window) and 1988 (small window). A typical fMRI acquisition (as of 2014) enjoys a range of spatial resolutions on the order of ≈ 0.5 —200 mm (i.e., from layers to whole brain coverage) and temporal resolutions on the order of few seconds to hours. Figure reproduced from Sejnowski, Churchland, and Movshon (2014), with permission.

time, fMRI has become a prominent neuroimaging modality in cognitive and systems neuroscience and has given rise to a new era of brain research, extending invasive approaches for measuring brain activity in animals to exploring the function and dysfunction of the living human brain (Sutterer and Tranel, 2017). The rise of fMRI to prominence coincided with an exponential increase in computer processing power, which has afforded neuroscientists with the means to ask and pursue fundamental questions about the human brain. Importantly, neuroscientists are now able to measure and begin to understand how the brain, with all its complexity, enable the mind and constrain behavior—a concept regarded as the "holy grail" of cognitive neuroscience. In this context, modern day neuroscientists use fMRI to explore different properties of brain activity during task performance and wakeful rest in relation to behavior across different populations. In a nutshell, brain activity can be measured by harnessing the temporal changes in regional cerebral blood flow (CBF) and blood oxygen level as markers of brain metabolism, which in turn is a surrogate of neuronal activity (Glover, 2011).

Prior to the development of neuroimaging, neuroscientists did not have an easy access to the living human brain in order to make inferences about the relationship between brain function and behavior. Early studies of brain-behavior relationships, from the 19th and early 20th centuries, mainly focused on brain physiology and lesions in animal models and local brain damage underlying a given behavioral syndrome in humans. Then, upon the death of a patient with brain damage, postmortem autopsies provided the confirmatory information about the site of the damage causing a specific syndrome, such as non-fluent or expressive aphasia; the famous Paul Broca's observation that speech deficits are caused by injuries targeting the left inferior frontal gyrus (Sutterer and Tranel, 2017). This observation, among many others at the time, fortified the belief in the existence of localized language centers in the human brain and later culminated in the emergence of the *functional localization/specialization* theory, holding that the brain is organized into spatially constrained and isolated regions each responsible of a specific function. Although sharply criticized, this school of thought has contributed to a better understanding of the functional organization of the brain and has found support in surgical neurology, anatomy, physiology, and electrophysiology (Finger, 2009; Friston, 2011). Of note, other pseudo-scientific approaches that advocated functional specialization existed such as phrenology that argued that personality could be determined by the local variations in the shape of the skull (Renneville, 2020).

The advent of MRI-based neuroimaging modalities, more than a century after Broca's observation, has paved the way for non-invasive and precise anatomical localization of functions in living patients with cognitive and behavioral deficits caused by brain injury and has significantly reduced the reliance on postmortem autopsies for inferring brain–behavior relationships (Karnath, Sperber, and Rorden, 2018). Moreover, the unprecedented combination of spatial and temporal resolutions provided by fMRI (Figure 2.1) has triggered a wave of studies focused on localizing brain regions, in healthy and diseased brains, that are active during the performance of a variety of tasks such as finger tapping (Biswal et al., 1995), language production (Binder et al., 1997), semantic memory (Hantke et al., 2013), working memory, visual attention (Tomasi et al., 2007), moral judgement (Greene et al., 2001) and executive functions (Sylvester et al., 2003), to name a few. The dominance of such studies in the early days of fMRI tacitly mirrored the early localizationist ambitions and the views of the brain as reflexive structure, driven by the momentary demands of the environment (Raichle, 2010; Sutterer and Tranel, 2017). This type of studies is still performed today (although not dominant anymore) and has significantly advanced our understanding of the function and dysfunction of disparate brain structures.

Yet, even with the use of non-invasive neuroimaging modalities, fundamental questions have always faced the localizationist and reflexive views of brain function. For instance, how modular is the functional organization of the brain with respect to functions? In other words, is there an accurate one-to-one map between functions and brain regions or is the coding more complex? Additionally, how are complex sequential behaviors (e.g., playing a piece on the piano) rapidly generated from highly specialized, segregated regions that are presumably discrete and do not interact? Moreover, how can the reflexive theory of brain function explain the brain's high energy expenditure in the absence of external task demands?

Unfortunately, task-activation fMRI experiments can reveal only a small fraction of the actual spectrum of functions performed by the human brain and cannot, alone, answer these fundamental questions (Raichle, 2010). Thus, there seems to be a discrepancy between how the brain has been traditionally thought to function and how humans actually behave and interact with their surrounding. Interestingly, a second wave of fMRI studies has quickly followed and dominated fMRI research, focusing on inter-regional interactions and brain networks as mediators and encoders of complex human behaviors, even in the absence of an externally directed task (Sutterer and Tranel, 2017). This has been motivated by a growing recognition in cognitive and systems neuroscience that frameworks focusing on singular neural substrates cannot account for all aspects of human behavior and brain disorders.

1.2 The Shift Towards Functional Integration

The localizationist view of brain function has been unable to explain how the brain incorporates and interprets information from multiple external and internal sources and give rise to complex behaviors and efficient cognitive processing. Therefore, it is highly unlikely that any region acts independently in isolation from the rest of the brain. This idea actually goes back to connectionist theories of the late 19th and early 20th centuries. These theories have advocated an integrative theory of brain function, which posits that complex brain processes are an emergent property of dynamic interactions among spatially distributed brain regions that form dense neural networks and operate in parallel (Benton, 1969; Sutterer and Tranel, 2017).

Early pioneers in neuroscience—such as Santiago Ramón y Cajal, Camillo Golgi, Carl Wernicke, and Korbinian Brodmann-were interested in understanding the laws that govern the central nervous system through network representations (Fornito, Zalesky, and Bullmore, 2016). For example, the famous Wernicke-Lichtheim network model of aphasia is among the very first macroscale representations of a network linking a language generation region (i.e., Broca's area) to a language comprehension region (i.e., Wernicke's area). However, at the time of Wernicke, due to methodological weaknesses and the reliance on postmortem autopsies to infer brain-behavior relationships, the progress of network approaches in neuroscience was slow and somewhat eclipsed by localizationist and psychological models of behavior and brain disorders (Fornito, Zalesky, and Bullmore, 2016). Nevertheless, the early diagrams of large-scale networks and later influential research work of Norman Geschwind on disconnection syndromes (Geschwind, 1974) have set the stage for the emergence and dominance of the **functional integration** theory and the concept of the **connectome**, which have been substantially supported by the development of electrophysiological and functional neuroimaging modalities, especially fMRI (Figure 2.2; see Cohen and D'Esposito (2016), Deco et al. (2015), Raichle (2010), Sporns (2013), and Varela et al. (2001) for comprehensive reviews).

Around the mid to late 20th century, the debate between the localizationist and

connectionist views had been gradually relaxing when it finally came into an uneasy balance that coincided with the early rise of fMRI as a predominant neuroimaging modality in the 1990s (Friston, 2011; Sutterer and Tranel, 2017). Shortly before that, however, it has been known that coordinated fluctuations in the neuronal activity of distributed brain regions are critical for complex behavior and higher-level cognition (Friston, 1994). In fact, at this point in time, a majority of neuroscientists has started advocating the **network theory** believed to combine localizationism, globalism (or holism), and disconnection theories into one ensemble (Figure 2.2). In particular, the theory posits that functions are localized to some degree in interconnected regions forming networks, the networks can be thought of as broad functional systems separately and collectively subserving a variety of functions, and the disconnection of different parts of a network induces heterogeneous effects based on the features of the isolated regions (Sutterer and Tranel, 2017).

These concepts have caught the attention of the nascent fMRI community, but have taken sometime to culminate into a promising field of research in fMRI. This is because the great success of task-evoked, localized brain activation studies, that briefly dominated the early days of fMRI, overshadowed efforts to map brain networks and understand their intricacies (Raichle, 2010). However, the past two and the half decades have witnessed a paradigm shift and a second wave of studies focused on functional networks and patterns of synchronized activity (i.e., connectivity) among distributed brain regions (Biswal et al., 1995; Fox et al., 2005; Van Den Heuvel and Pol, 2010). These studies rely on the concepts of *functional* and *effective connectivity*, previously used in EEG and PET studies, to quantify functional integration among remote regions in the brain (see Friston (1994) and Friston (2011) for reviews on the topic).

Functional connectivity (FC) has been, and still is, the predominant measure of functional integration and is formally defined as the temporal correlation (or statistical dependence) between remote neurophysiological events (i.e., neuronal signals, changes in CBF and oxygen level) recorded simultaneously in distinct brain regions, whereas effective connectivity is defined as the magnitude of directed causal influences that neural populations exert over another (Friston, 2011). These measures have provided the much needed platform to explore how information is allocated



FIGURE 2.2: Complex network topology (left) arises from a balance between a high-cost, largely integrated workspace (top stream) that supports fluid intelligence, problem solving, planning, executive functions, and effortful information processing; and segregated modules (bottom stream) specialized, automated, and unconscious information processing. Figure reproduced from Fornito, Zalesky, and Bullmore (2016), with permission, Copyright (2016) Elsevier Inc., London, UK

and processed in the brain and manifest as complex behaviors, and how does the brain's network organization vary as function of age, gender, learning, task conditions, and brain disease (Van Den Heuvel and Pol, 2010). Studies of fMRI FC have revealed interesting findings of the functional repertoire of different large-scale networks as well as their hierarchical topology, spatial and temporal dynamics, and disturbances across brain disorders (Buckner, Krienen, and Yeo, 2013; Fox et al., 2005; Lurie et al., 2020; Van Den Heuvel and Pol, 2010). Perhaps one of the fundamental discoveries in this area is that regions that are active together during the task performance maintain signatures of their interactions that can be detected during rest (Biswal et al., 1995). This discovery has opened a window for new research perspectives in cognitive and systems neuroscience and paved the way for the discovery of a cognitively rich intrinsic network architecture in the "resting" brain,

which in fact reflects a "restless brain" (Biswal et al., 1995; Raichle, 2011).

1.3 The Restless Brain

The living human brain exhibits an ongoing "stream of consciousness" regardless of the presence or absence of an explicit behavior (Raichle, 2011). In fact, this idea of a "restless brain" has philosophical roots in ancient history. Around the year 60 CE, the Roman stoic philosopher Seneca stated: "The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is... far from restful" (Seneca, 2016). Centuries later, in the late 1800s, William James stated: "Whilst part of what we perceive comes through our senses from the object before us, another part (and it may be the larger part) always comes out of our own mind" (James, 2007). Shortly after James, a number of neuroscientists argued that the brain is not primarily reflexive, but rather exhibits an intrinsic function beyond simple responses to stimuli (Raichle, 2010). However, these claims were given little credence at the time. Many years after Seneca and James, and with the development of electrophysiological recording, optical imaging, MR spectroscopy, PET, and ultimately fMRI, neuroscientists have detected spontaneous yet strikingly coherent fluctuations in brain activity while subjects rested in a state of mind wandering. However, the discovery of this remarkable property of brain activity had been motivated, in large, by questions of neurobiology before being harnessed by cognitive theories (see Raichle (2010) and Snyder and Raichle (2012) for comprehensive historical reviews).

In the early to mid 20th century, scalp EEG and averaged evoked response potentials have enabled researchers to extract reproducible waveforms of ongoing brain activity and relate them to external stimuli (Snyder and Raichle, 2012). Although the pioneers of EEG understood that explicit "mental activity" only slightly increments cortical work which is already going on continuously (Millett, 2001), almost all of the research work carried using EEG has been based on phase synchrony between extracted waveforms and external events of interest (Snyder and Raichle, 2012). Interestingly, around the same time period, seminal studies focusing on whole-brain metabolism in resting state have revealed that the brain, while contributing to only 2% of the body weight, consumes around 20% of the body's



FIGURE 2.3: Resting-state fMRI studies have converged on a set of large-scale resting-state networks (RSNs) that are reproducible across healthy and diseased individuals. Of those networks is the default mode network (DMN; top-left) that subtends the posterior cingulate cortex, the medial prefrontal cortex, and angular gyrus. This RSN is active during mind wandering, daydreaming, planning the future, and remembering the past. This figure adapted from Raichle (2011), with permission.

energy (Sokoloff et al., 1955). Later studies using similar approaches have revealed that the energy expenditure of the brain during "mental activity" is too low (compared with resting state) to be detected, and that the resting state accounts for the majority of the brain's metabolic costs (Snyder and Raichle, 2012; Sokoloff et al., 1955). Moreover, long before fMRI, studies of spontaneous fluctuations in regional oxygen concentration have reported low-frequency (< 0.1 Hz) variations in oxygen levels that are synchronous in homologous regions in both brain hemispheres and increase with the presentation of an external stimuli (Cooper and Crow, 1975; Snyder and Raichle, 2012). These early findings, among others, have confirmed that the resting brain is actually not in a "resting state", in the literal sense. Nevertheless, up until cognitive neuroscientists started using functional neuroimaging modalities, it

was not clear how to undertake a study of spontaneous brain activity to infer brainbehavior relationships and understand the organizational principles of the human brain.

With the development of fMRI, evidence of spontaneous brain activity and, consequently, inter-regional FC in subjects lying still in an MRI scanner, has affirmed, without any doubt, the presence of a spatially organized and cognitively rich spontaneous activity in the human brain. The first attempt to explore spontaneous activity and resting-state FC using fMRI was in a study by Biswal et al. (1995) who reported that low frequency, spontaneous fluctuations (< 0.1Hz) in activity of the left and right primary motor cortices highly synchronize with each other and also with those in other brain regions. This seminal study has revealed, for the first time, that a considerable fraction of the spontaneous fluctuations (previously regarded as noise) exhibits patterns of signal coherence within known brain systems. Interestingly, these resting state patterns strikingly mirrored those observed when subjects performed a finger tapping task (Biswal et al., 1995). In the decade following these findings, resting-state fMRI (rsfMRI) would become one of the core research approaches used by neuroscientists to evaluate inter-regional FC in the brain (Buckner, Krienen, and Yeo, 2013). In this context, studies have found that individual differences in resting state FC can predict phenotypic traits (Smith et al., 2015), cognitive performance (Rosenberg et al., 2016), age, gender, and even individual identity (brain "fingerprinting"; Finn et al., 2015). Despite its many limitations, such as the sensitivity to physiological noise and in scanner head motion and the lack of control over an individual's cognitive state, rsfMRI has proven to be well-suited for exploring the brain's functional organization, inferring brain-behavior relationships, and extracting relevant biomarkers for brain disorders (Greicius, 2008; Ichikawa et al., 2017; Liégeois et al., 2019; Smith et al., 2015).

A great advantage of rsfMRI over task-based fMRI experiments, which typically highlight a single brain network or region associated with a task, is that they provide a means to explore multiple functional networks at once, with minimal constraints and enhanced analytic flexibility (Lv et al., 2018). As a result, studies of resting state FC have converged on a set of large-scale networks (Figure 2.3) characterized by strong intraconnections and weaker interconnections. These canonical
modules, commonly known as resting-state networks (RSNs), form the backbone of global brain connectivity, are consistently detected across populations, and highly correspond with task-evoked co-activation patterns (Figure 2.5; Calhoun, Kiehl, and Pearlson (2008), Damoiseaux et al. (2006), Power et al. (2011), Rosazza and Minati (2011), Smith et al. (2009), and Yeo et al. (2011)). Moreover, these networks exhibit a hierarchical organization transcending single-resolution maps showing large-scale RSNs. For instance, using clustering techniques on rsfMRI, Schaefer et al., 2017 have been able to generate up to 1000 functionally homogeneous regions in the cerebral cortex (Figure 2.4) that, when grouped together, highly overlap with large-scale brain network organization (7 or 17 networks) previously identified by Yeo et al. (2011) in a large dataset of healthy individuals.

One of the most intriguing and highly-studied networks is the default mode network of the brain, or the DMN. First discovered by Shulman et al. (1997) using PET and then by Raichle et al. (2001) using rsfMRI, the DMN, or the "task-negative" network, is activated when individuals focus their attention on internally oriented tasks such as daydreaming, planning the future, processing personal/familial information, retrieving autobiographical memories, and gauging the perspectives of others (Raichle et al., 2001; Greicius et al., 2003). More RSNs that subserve other brain functions including executive-control, attention, language, salience, visual, sensorimotor, auditory, and limbic networks have been identified (Buckner et al., 2011; Choi, Yeo, and Buckner, 2012; Fox et al., 2006; Dosenbach et al., 2006; Power et al., 2011; Seeley et al., 2007; Yeo et al., 2011). Importantly, it has been shown that these networks reflect a history of co-activation among distributed regions across a wide range of tasks and encode various aspects of behavior and cognition (Barkhof, Haller, and Rombouts, 2014; Calhoun, Kiehl, and Pearlson, 2008; Liégeois et al., 2019; Smith et al., 2009). Moreover, the RSNs are believed to emerge from complex organizational mechanisms and exhibit multiscale spatiotemporal changes as a function of age, awareness, learning, arousal, and task conditions (Chang and Glover, 2010). As a result, a large body of literature has been devoted to explore the principles underlying the emergence of RSNs, their communication routes, and the roles they play in complex cognitive processes (Power, Schlaggar, and Petersen, 2014). This has required the integration of a wide array of analytical approaches



FIGURE 2.4: The influential Yeo 7 and 17-Networks map of the functional organization of the cerebral cortex, each represented by a different color (first row). Second row shows each functional region from Schaefer et al. (2017) assigned a network color based only on spatial overlap with networks from Yeo et al. (2011). Clustering of parcels without prior reference to Yeo's 7 and 17 Networks shows striking similarity between second and third rows, suggesting a hierarchical functional network structure in the brain during resting state. Figure reproduced from Schaefer et al. (2017), with permission.

that have afforded modern day neuroscientists an unprecedented opportunity to explore the intricacies of the intrinsic functional network organization of the human brain.

1.4 Contemporary Trends and Future Perspectives

Understanding the organizational principles that give rise to brain networks and, ultimately, complex human behavior is the crux that drives the search for refined models of the human brain. In this context, the recent convergence of the opposing



FIGURE 2.5: RSNs highly resemble task activated networks (left side and right side of **(A)**, respectively). **(A)** Rest and task-evoked networks reported in Smith et al., 2015. Networks are: (1) medial visual, (2) occipital visual, (3) lateral visual, (4) default mode, (5) cerebellum, (6) sensorimotor, (7) auditory, (8) frontal executive/salience, (9) right frontoparietal, and (10) left frontoparietal. **(B)** Sensorimotor network during finger tapping task (top) and during resting-state from the seminal resting-state fMRI study by Biswal et al. (1995). Figures adapted from Barkhof, Haller, and Rombouts (2014) and Biswal et al. (1995), with permissions.

views of brain function has motivated neuroscientists to model the brain as a complex interconnected system with **small-world** properties that supports both specialized and distributed processing of information and transcends multiple levels of space, time, and topology (Achard et al., 2006; Bassett and Bullmore, 2006; Bassett and Bullmore, 2017; Betzel and Bassett, 2017; Bullmore and Sporns, 2009; Sporns, 2018). Roughly speaking, a network is said to have small-world properties if any two of its components can efficiently communicate and share information through a short sequence of connections (Achard et al., 2006). Another important property that is highly associated with small-world networks is the over-abundance of network *hubs*, which are network components that play multiple roles and enable efficient signaling within the network through strategic short-range connections with many network components (Achard et al., 2006; Crossley et al., 2014; Heuvel and Sporns, 2013). These ideas are not totally new to neuroscience; in fact, Santiago Ramón y Cajal was among the first neuroscientists to anticipate these aspects of brain network architecture (Fornito, Zalesky, and Bullmore, 2016). He believed that the morphological confirmations of neurons are governed by laws of conservation of time, space, and material. However, at the time of Cajal, apart from delineating small sets of anatomical neural connections, it was not possible to measure how the brain combines two archetypal extremes that can, ultimately, give rise to efficient, ongoing cognition from the integration of discrete sets of external and internal information (Achard et al., 2006; Bassett and Bullmore, 2006).

In recent times, this representation of the brain experienced a theoretical and computational revolution that is breaching neuroscience research, allowing neuroscientists to explore the overwhelming complexity of the human brain across multiple scales and dimensions and model its structure and function from new perspectives, sometimes combining them together (see Huang and Ding (2016) for a review). The advances in fMRI technology in terms of spatial and temporal resolutions, along with unprecedented advances in automated mathematical tools, such as graph theory and machine learning, have enabled neuroscientists to begin understanding the multiscale properties of the human brain (Betzel and Bassett, 2017). On one hand, graph theory has simplified the analysis of highly detailed brain systems by providing simple graphical models, implemented using simple mathematical language, by which myriad biological intricacies of the brain are effectively reduced to a set of vertices or **nodes**, representing brain regions, connected by lines or **edges**, which represent connectivity (Fornito, Zalesky, and Bullmore, 2016). The application of graph theory to rsfMRI data has revealed non-trivial topological properties of the intrinsic network organization of the human brain (Fornito, Zalesky, and Bullmore, 2010; Fornito, Zalesky, and Bullmore, 2016; Wang, Zuo, and He, 2010). Among these is that the brain is a resilient, small-world, and modular network with a rich-club (i.e., hubs) organization that promotes efficient information allocation (Achard et al., 2006; Van Den Heuvel and Sporns, 2011; Sporns, 2018).

On the other hand, studies using machine learning to project high-dimensional resting-state FC data onto a low-dimensional space have revealed representational gradient-like hierarchies of information processing ranging from specialized unimodal regions to integrative transmodal regions (primary-unimodal-transmodal hierarchy; Figure 2.6; Huntenburg, Bazin, and Margulies, 2018; Sepulcre et al., 2012;



FIGURE 2.6: Cortical FC gradients 1–3 of the human brain. **(A)** Gradient 1 is the principal axis of connectivity variation and extends from the primary sensorimotor regions (blue) to transmodal default mode regions (red). **(B)** Gradient 2 extends from somatomotor/auditory cortices (blue) to the visual cortex (red). **(C)** Finally, gradient 3 extends from default mode and sensorimotor regions to executive control regions. Figure adapted from Margulies et al. (2016).

Guell et al., 2018; Margulies et al., 2016; Mesulam, 1998). The theory of **functional gradients** is a new frontier in the field of human brain mapping, promising to reveal how the spectrum of cognitive functions emerges from the spatial arrangement of the brain's functional modules (Margulies et al., 2016; Huntenburg, Bazin, and Margulies, 2018). The theory posits that, although the brain is formed of functional networks of strongly interconnected regions, the spatial arrangement of these is not arbitrary nor defined by strict borders, but rather by smooth gradients that reflect a gradual transition of information processing from specialized primary cortices to multiple demand domain-general systems and, ultimately, to highly-integrative brain regions that are "insulated" from direct environmental input and hence support abstraction of information in the form of emotions, memories, and social interactions (Huntenburg, Bazin, and Margulies, 2018; Margulies et al., 2016; Sepulcre et al., 2012). Importantly, the spatial location of a brain region along these gradients can determine its functional role (Huntenburg, Bazin, and Margulies, 2018).

Since the early beginnings of fMRI research and up until the early 2010s, almost all studies have summarized brain FC over the entire scanning session using a single measure of dependency per pair of regions, such as correlation or coherence. This approach has been used to identify stable large-scale networks in the brain and characterize their dominant FC patterns. Additionally, FC averaged over extended periods of time has been shown to correlate with the structural connectivity between brain regions (Wang et al., 2013). However, the brain is a complex

multiscale system (Lurie et al., 2020), and in order to adapt to constantly changing environmental conditions or experimental task demands, it must rapidly reconfigure its network structure and integrate neuronal ensembles in a flexible yet contextual manner (Zalesky et al., 2014). This physiological reality adds an extra dimension to the functional organization of the brain; it allows the brain to optimally process multiple inputs and execute complex cognitive processes in a timely manner through temporal transitioning across a set of recurring network configurations, or states (Figure 2.7), each characterized by a whole-brain FC pattern, a spatial co-activation pattern, a probability of activation/occurrence (Vidaurre, Smith, and Woolrich, 2017). The time-varying, transient patterns of FC, observed using fMRI, are believed to index changes in activity at the neuronal level (Hutchison et al., 2013). Moreover, it has been shown that dynamic or time-varying FC (TVFC) predicts personality traits (Liégeois et al., 2019), learning capabilities (Bassett et al., 2011), attention (Madhyastha et al., 2015), cognitive flexibility (Douw et al., 2016), creativity (Li et al., 2017), and emotional regulation (Betzel et al., 2017), and to exhibit alterations in brain disorders (Braun et al., 2016; Damaraju et al., 2014; Rashid et al., 2014; Sakoğlu et al., 2010).

With the fast accumulation of evidence on TVFC, the fMRI community grasped that previous studies have been limited by the assumption of spatiotemporal stationarity of FC over the scanning session (Calhoun et al., 2014). As a result, the second decade of the twenty-first century witnessed a third wave of studies that shifted from time-averaged measures of FC, to measures of TVFC. This conceptualization has culminated in the emergence of the field of *dynamic functional connectivity* as opposed to the field of traditional methods known as *static functional connectivity*. However, like any emerging field of research, TVFC analysis still suffers from continuous debates, inaccuracies, and controversies regarding the extent to which the estimates reflect actual changes in neuronal signaling or the extent to which these estimates are driven by an actual change in cognitive state and not by background noise (e.g., head motion or cardiovascular and respiratory effects) or sampling variability (see Lurie et al. (2020) for a review on the topic). Moreover, it still not clear how to determine if the observed estimates of TVFC are actually "time-varying" compared with "static" null hypotheses, and what are the properties that define a true "dynamic" FC (Liegeois et al., 2017). Furthermore, fundamental questions often arise regarding how the time-varying integrative topology of the brain fits into the model of conservation laws and the theory of brain-wide processing hierarchies. These questions and criticisms suggest that the field is still in its infancy. However, despite these difficulties, the time-resolved analysis of FC stands out as an attractive tool with great potential to expand our understanding of brain dynamics and is likely to remain a promising research frontier in the future (see Calhoun et al. (2014), Hutchison et al. (2013), Keilholz (2014), Lurie et al. (2020), and Preti, Bolton, and Ville (2017) for reviews).



FIGURE 2.7: Spontaneous brain activity measured by fMRI has been found to transition between a set of recurring states each characterized by a unique patterns of functional connectivity (Bottom Panel), a spatial co-activation pattern among brain regions (Middle Panel), and a probability to be active at timescales shorter than the duration of an fMRI scanning session. Figure reproduced from Vidaurre, Smith, and Woolrich (2017).

The impact of fMRI on neuroscience has been marked by the old-new debates and paradigm shifts from localizationist/reflexive to integrative/intrinsic views,

and recently to brain-wide functional hierarchies that extends beyond single scales of topology, time, and space. Despite the limitations of fMRI, such as the limited temporal resolution, the uncertainty of neurobiological interpretations of FC, and issues of reliability and reproducibility (see Elliott et al. (2020) for a recent review), there is no doubt that the rich fMRI-based literature has provided an incredible amount of knowledge about the living human brain. In fact, the comprehensive mapping of functional systems in the healthy and diseased brain has created an abundance of data on the human connectome. As a result, functional neuroimaging modalities in general, and in particular fMRI, are rapidly transforming neuroscience into the era of "big data". In this context, several large-scale initiatives have been created to collect and curate high-quality fMRI data from hundreds and thousands of individuals. These initiatives include, but are not limited to, the Human connectome project (Van Essen et al., 2013), UK Biobank Imaging Study, Brain Genomics Superstruct Project (Buckner et al., 2012), Midnight Scan Club, and MPI-Leipzig Mind-Brain-Body database (Mendes et al., 2019), to name a few. However, these population imaging protocols entail massive data storage. Thus, online platforms for sharing and organizing multilmodal imaging databases including MRI, MEG, EEG, iEEG, and ECoG data have been created to accommodate such largescale datasets (Gorgolewski et al., 2017). Additionally, another kind of platforms have emerged, such as NeuroSynth, that aim at creating a generative framework for automatically synthesizing human fMRI data to distil the extant literature and achieve a consensus regarding the relationship between brain structure, function, and observed behavior (Yarkoni et al., 2011). The long-term goals of these initiatives include constructing the human brain connectome, promoting open neuroscience, informing brain-inspired artificial intelligence, and contributing to the development of novel strategies for diagnosis, treatment, and prognosis of brain disorders.

2 Bases of fMRI: From 3D to 4D Images

2.1 Physical Basis of MRI

The complex physics behind MRI and, consequently, fMRI boils down to the interaction between strong magnetic fields and protons of atoms that make up biological tissues. Conventional MRI scanners apply a strong and static magnetic field (1.5, 3, or 7 Tesla) to align the magnetic spin moments of protons along an axis parallel to the direction of the field, around which they "precess" or rotate in particular frequency. Then, a second magnetic field, known as the gradient field, is applied in order to define the position, in three dimensional (3D) space, of the protons. This gradient field distorts the main field in a predictable pattern, inducing gradual variations in the resonance frequency of protons as a function of their position in space. Finally, radio-frequency (RF) excitation pulses are emitted to excite the protons to higher magnetization levels, creating the nuclear magnetic resonance condition by which protons absorb energy. When the RF field is removed, the protons go back to their equilibrium or "relaxed" states along the axis of the main magnetic field and emit electromagnetic radiation (i.e., MR signals) that are recorded using a special coil and later reconstructed in the form of high-resolution 3D images of the brain (Figure 2.9). The time required for the magnetization of protons to relax varies from one tissue type to another depending on their constituent elements and the corresponding number of protons. This difference in relaxation times can be used to produce contrast among different types of brain tissues. Thus, conventional MRI scans provide static, high resolution 3D images of the brain, which allow clinicians and neuroscientists to explore different properties (e.g., volume, shape, etc..) of brain structures and detect damage caused by strokes or tumors. See Ogawa et al. (1990) and Wang (2014) for a comprehensive overview of the physics of MRI.

2.2 Bases of fMRI

The central idea underpinning the development of fMRI is to extend conventional MRI brain scans beyond capturing static 3D images to capturing the temporal

changes in regional brain metabolism/activity in a 3D+time, or 4D, fashion as proxies to neuronal activity. The physical and physiological bases underlying fMRI, in its most prevalent form, are based on the blood-oxygenation-level-dependent (BOLD) effect occurring through the process of hemodynamic response that follows a neuronal activity (i.e., "firing") combined with the differential physical properties of hemoglobin. The physiological relationship between brain activity and blood flow has been around since the late 19th century and was first proposed by Roy and Sherrington (1890) who stated that "...the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity...". However, the basis of temporal coupling between cerebral blood flow (CBF) and brain activity now rests on physiological findings, from the 20th century, holding that neurons, when firing, rapidly consume available energy and require that oxygen and nutrients be rapidly and continuously delivered by the CBF (Figure 2.8A); a phenomenon known as neurovascular coupling (see Attwell and Iadecola (2002), Buxton and Frank (1997), and Hosford and Gourine (2019) for reviews on the topic). When neurons fire as a response to external or internal stimuli, the hemodynamic response to the neuronal activity induces a rapid delivery of blood oxygen to active neurons at a greater rate than consumed (Raichle and Mintun, 2006). This causes the amount of oxygenated blood (i.e., oxyhemoglobin) arriving to the site of activity to significantly increase with respect to the amount of deoxygenated blood (i.e., deoxyhemoglobin) present as a result of oxygen consumption. This causes a relative difference in the levels of oxyhemoglobin and deoxyhemoglobin that is detected on the basis of the differential magnetic properties of hemoglobin.

Hemoglobin has a varying sensitivity to magnetic fields, depending on whether it is bound to oxygen molecules or not (Raichle and Mintun, 2006). Particularly, deoxyhemoglobin is paramagnetic (i.e., it is more attracted to magnetic fields), whereas oxyhemoglobin is diamagnetic (i.e., it is less responsive to magnetic fields). Thus, deoxyhemoglobin alone distorts the surrounding magnetic field, causing



FIGURE 2.8: **(A)** Cerebral blood flow (CBF) delivers oxygen to "inactive" (left) versus active (right) neurons. **(B)** The canonical hemodynamic response function (HRF). As illustrated in B, after the presentation of a stimuli, an initial dip in the HRF occurs, followed by a fast rise, peak, a gradual fall, and, finally, a brief "undershoot" where the MR signal falls below baseline level. Following the onset of neuronal activity, an initial dip (1–2 s) occurs, reflecting a brief decrease in the MR signal and an initial increase in the proportion of deoxyhemoglobin to oxyhemoglobin due to fast consumption. Shortly following this local oxygen deficit, an inflow of oxygenated blood supplies significantly more oxygen than is consumed to support neuronal activity. This results in a decrease in the ratio of deoxyhemoglobin to oxyhemoglobin and a fast increase in the MR signal, peaking at around 4–6 s following neuronal activity. When neuronal activity ceases, the CBF will return to baseline levels while blood volume will remain elevated. This combination result in a transient increase in the ratio of deoxyhemoglobin to oxyhemoglobin to oxyhemoglobin, reflecting a post-stimulus undershoot of the MR signal.

nearby protons to lose their magnetization much faster and emit a weak MR signal. In contrast, a local increase in oxygen delivery over oxygen consumption decreases the concentration of deoxyhemoglobin, thereby reducing local field inhomogeneities and enhancing the emitted MR signal. These subtle differences in the magnetic properties of hemoglobin form the bases of the BOLD contrast that allow neuroscientists to produce brain activation maps of neuronal assemblies that exhibit a relative increase/decrease in activity compared with those that are "inactive" (i.e., remain at baseline activity) during task performance or wakeful rest. For a comprehensive overview of the physiological basis of fMRI, see Buxton and Frank (1997), Buxton, Wong, and Frank (1998), Glover (2011), Hosford and Gourine (2019), and Ogawa and Lee (1990).



FIGURE 2.9: Conventional MRI scans (left) produce a single high-resolution 3D volume, whereas fMRI scans (right) produce a series of 3D volumes that reflect changes in brain metabolism/activity with relatively lower spatial resolution than conventional scans.

2.3 Data Acquisition

In conventional MRI, the contrast in the image depends on the differential relaxation times of protons in different brain tissues after the removal of the RF-pulses. Specifically, the contrast can be characterized by two relaxations times: T1 (longitudinal relaxation time), which measures the time of the exponential return of magnetization to equilibrium, and T2 (transverse relaxation time), which measures the time of exponential decay of phase synchronization between the magnetic spin moments of protons while their magnetization is returning to equilibrium. T2 is much shorter than T1 in human tissue, and local differences in the main magnetic field, caused by machine inaccuracies and differential brain anatomy, induces even a faster decay in phase synchronization, commonly known as the T2* relaxation time. T1, T2, and T2*-weighted images can be used to explore different contrasts between different types of tissues depending on the question and application. In this context, fMRI makes use of the local differences in magnetization (i.e., BOLD contrast) and therefore requires the acquisition of T2*-weighted images (Weisskoff et al., 1994).

The acquisition of BOLD-fMRI data with whole-brain coverage requires the collection of multiple 3D brain volumes (i.e., images) to obtain a single 3D+time image of brain activity per scanning session. In standard fMRI protocols, volumes are collected using fast echo-planar imaging (EPI), which allows for a rapid collection of single or multiple 2D brain slices and stacking them to create the 3D image or volume. The 3D image consists of an array of volumetric pixel (or voxel) intensity values, one value per voxel, that encode the activity of the underlying cluster of neurons. In order to obtain 3D+time (or 4D) data that capture the temporal changes in brain activity, gradient echo (or spin echo) RF excitation pulses are applied in short time intervals, and by the end of each interval a 3D image is collected. This procedure yields a timeseries of T2*-weighted 3D brain images (Figure 2.9) and takes about 0.5 to 4 seconds per 3D volume; a duration known as the repetition time, or simply TR. Thus, a 15-minute (900 seconds) fMRI scan with a TR=2 seconds yields a timeseries of 450 T2*-weighted (i.e., BOLD) 3D volumes that capture temporal changes in brain activity as a response to stimuli and task conditions or during resting state. For detailed explanations of the physical and technical principles of MRI and fMRI, the reader is referred to the broad literature and many textbooks on the subject, such as Bernstein, King, and Zhou (2004), Westbrook (2014), and Wang (2014).

3 Preprocessing of fMRI Data: Going Through the Artifacts

The BOLD-fMRI data are complex mixtures of neuronal, metabolic, and vascular processes, severely affected by non-neuronal noise of instrumental and physiological origins, such as low frequency drifts, respiration, heart beat, and most infamously, head motion (Power et al., 2012). As a result, a certain form of preprocessing must be performed to "denoise" and normalize the data before subjecting it to further analysis. The preprocessing of fMRI data is typically performed in a sequence of steps forming a pipeline that is usually paralleled by another pipeline for structural MRI images (Esteban et al., 2019). Over the years, many strategies to counteract and adjust for different noise sources have been developed. So far, however, there is still no consensus in the preprocessing stage regarding the most effective pipeline. Nonetheless, preprocessing is necessary in one form or another to attenuate unwanted artifacts as much as possible and transform the data into a standard format. Here, the commonly used preprocessing steps and the type of artifact they tackle are briefly described. Note that only volume-based preprocessing techniques are discussed in the following subsections. For a comprehensive overview of the merits and pitfalls of different fMRI preprocessing steps, pipelines, and tools, the reader is referred to specialized research work on the topic, such as (Ciric et al., 2017; Jenkinson and Smith, 2006; Patel et al., 2014; Poldrack, Mumford, and Nichols, 2011; Power et al., 2012; Power et al., 2014; Soares et al., 2016).

3.1 Pre-preprocessing

The raw images collected during an fMRI scan are typically stored in the DICOM (Digital imaging and communications in medicine) format before being converted to the NIFTI (Neuroimaging Informatics Technology Initiative) format for analysis. Then, there are some "zeroth" steps that have to be completed before subjecting the data to further preprocessing and may include preliminary re-orientations of images, brain extraction (i.e., "skull-stripping"), tissue segmentation of the T1-weighted structural images, bias field corrections, and the removal of the first few

volumes. The latter step is important as it usually takes around five to eight seconds for protons to approach a steady state after the magnetic fields are applied, and thus the volumes acquired during the first few seconds (\approx 5 to 10 seconds), also known as non-steady state scans, are removed. However, most modern MRI scanners automatically discard the non-steady state scans from the raw data (Gonzalez-Castillo et al., 2013).

3.2 Distortion Correction

The use of fast EPI makes the fMRI data sensitive to inhomogeneities in the main magnetic field that cause unwanted geometric distortions, which are not uniform across subjects and brain regions and are more severe in some regions than others, especially in the orbitofontal cortex and the medial temporal lobe (Chang and Fitzpatrick, 1992; Chambers et al., 2015). Magnetic field inhomogeneities are not known in advance and highly depend on the geometry of individual brains, the orientation with respect to the main magnetic field, and other machine-specific settings. Modern MRI scanners can minimize these effects by fine-tuning the magnetic fields in a procedure known as shimming. However, it is necessary to account for inhomogeneities that are not adjusted for by shimming. In this context, magnetic field inhomogeneities can be measured using "fieldmapping" techniques that require the acquisition of two gradient echo images with slightly different echo times (i.e., onset of RF-pulses) or EPI images with different phase-encoding directions and calculating a map of the phase differences between them (Jezzard and Balaban, 1995).

The phase difference image which is proportional to the magnetic field strength at any given location. That is, in the ideal case of a completely uniform and homogeneous magnetic field the phase difference induced by the different echo times (or phase-encoding directions) will be the same across all voxels and hence no geometric distortion of voxels is detected. Using the phase difference image, one can generate a fieldmap the measures the degree of distortion of voxels and then apply an equal and opposite "shift" to the fMRI data (Jezzard and Balaban, 1995; Wang et al., 2017). This preprocessing step is often called **distortion correction** or **fieldmap** **unwarping** and has two advantages: **(a)** improving the within-subject similarity between the fMRI functional images and the high-resolution MRI structural images; and **(b)** reducing the non-uniformity of geometrical distortions across subjects to improve the spatial mapping of individual brain images onto a common brain template in group-level designs. Finally, several effective "fieldmapless" techniques have been recently developed to estimate the distortion using nonlinear image registration and can be used with some confidence in case fieldmap images have not been collected during the scanning session (see Chambers et al. (2015), Chang and Fitzpatrick (1992), Hutton et al. (2002), Jezzard and Balaban (1995), and Wang et al. (2017) for reviews on the topic).

3.3 Slice Timing Correction

The first step of preprocessing after distortion correction is conventionally slice timing correction, even though some studies prefer to perform this step before correcting for geometrical distortions. In short, MRI scanners acquire several 2D slices, via fast EPI, at slightly different instances in order to construct a single 3D volume and, subsequently, a 4D image of the brain. Thus, brain activity in one 3D brain volume might be presented at slightly different instances across 2D (Figure 2.10), which can complicate later analysis. Exact timing is essential for fMRI data analysis to accurately model the effects of different stimuli. Thus, slice timing correction is performed using interpolation techniques to correct those timing differences between acquired slices. However, slice timing correction is not recommended if the repetition time (TR) is in the sub-seconds (< 1 s).

3.4 Motion Correction

In a typical fMRI session there will be inevitable head movements that severely corrupt the data with artifacts and noise (Friston et al., 1996). Head movements in the scanner cause the voxel-to-neurons mapping to vary from one volume to another while scanning is in progress. That is, a voxel may continue to refer to the same absolute location in space while the neurons underneath it have changed. Thus, **motion correction** is crucial in order to establish spatial correspondence across brain



FIGURE 2.10: Slice Timing correction involves shifting the data acquired at slightly different instances via interpolation to account for slice timing differences MRIQuestions.

volumes. Motion correction operates by selecting one functional volume (usually the first or middle one) as a reference to which all other functional volumes are aligned via rigid-body transformation (Frackowiak et al., 2004; Jenkinson et al., 2012; Jenkinson et al., 2002). The rigid realignment improves the spatial correspondence between scans such that voxels correspond to the same brain regions and locations across different volumes. In rigid-body transformation, spatial displacement of volumes is described by three translation parameters along the x, y and z-axes in 3D space and three rotation parameters around these axes as well. These six parameters are estimated iteratively by analyzing how a volume has been translated and rotated so that it is aligned with the reference volume. Moreover, the six motion parameters can be used in the calculation of the frame-to-frame movement, or the *framewise displacement* (FD), which can be used to inform exclusion criteria of high motion subjects to further adjust for motion-induced spurious findings in

group designs (Power et al., 2014).

3.5 Coregistration and Spatial Normalization

Typical fMRI studies collect data from multiple subjects that differ in terms of head size and shape. Such inter-individual variability in brain structure precludes grouplevel inferences in terms of regional correspondence of activity and functional connectivity from one subject's brain to another. Therefore, to uniformly interpret the results across subjects, studies use a standard brain template, and systematically transform all the subjects' data (structural and functional) to the coordinate system of this template, also known as the standard space. This preprocessing step is known as **spatial normalization**. The commonly used standard templates are the Talairach template, which is a single brain image of an elderly woman created by Jean Talairach in 1967 (Talairach and Szikla, 1980), and the Montreal Neurological Institute (MNI) template, commonly known as MNI152, which is a probabilistic brain map that has been created by combining and averaging high-resolution structural MRI brain images of 152 healthy individuals (Laird et al., 2010; Mazziotta et al., 1995).

Normalizing T1-weighted structural images to the standard space can be directly performed using automated non-linear *affine transformation* or diffeomorphic non-linear registration techinques (Avants et al., 2011). However, transforming the functional images into the standard space cannot be performed directly, because functional images have a much lower spatial resolution and inter-tissue contrast than structural images and may suffer from intensity distortions. Therefore, to define regions of interest and localize brain activity within individual brains with some confidence, one needs to align the subject-specific functional images with the same subject's MRI structural T1-weighted image prior to spatial normalization. This step is known as **coregistration**. Coregistration is usually performed using six-, nine-, or twelve-parameter rigid-body transformation, similarly to motion correction. After coregistration, the spatial normalization to the standard space can be achieved by applying the transformations, obtained from the normalization of the T1-weighted images to the standard space, to the T1-coregistered functional images to obtain normalized fMRI data across all study subjects (Figure 2.11). However, it is recommended to apply the different resampling or deformation steps (i.e., distortion correction, motion correction, coregistration, normalization) to the raw BOLD data in a single step after concatenating all the pertinent transformations (initially estimated using a reference 3D BOLD volume) into one transformation matrix or deformation field such that little information is lost due to multiple resampling of the raw data (Esteban et al., 2019).



FIGURE 2.11: Flowchart of a standard pipeline to normalize fMRI data. (1) motion correction by realignment, (2) coregistration of structural and functional images, (3) normalization of structural images to a standard anatomical space (e.g., MNI152 space), (4) Apply the deformations from the previous to the structurally-coregistered functional images, and finally (5) Smoothing of the functional images using a Gaussian Kernel. Figure reproduced from Flandin and Novak (2020), with permission.

3.6 Spatial Smoothing

After spatial normalization, many studies choose to apply **spatial smoothing** to the spatially normalized fMRI data to enhance the signal-to-noise ratio (SNR) and average out spatially distributed high-frequency noise in each volume. Spatial smoothing consists of averaging each voxel intensity with the intensity of nearby voxels to

produce a smooth spatial map across the brain (Figure 2.12). Averaging is achieved by convolving the data with a Gaussian kernel (or filter), which, at every voxel, weighs neighboring voxels by their distance, with the weights decaying exponentially according to a bell curve shape. The Gaussian kernel is characterized by its "Full Width at Half Maximum" or, simply, *FWHM* measured in millimeters. The *FWHM* is related to the standard deviation of the Gaussian filter and usually takes the values 2, 4, 6, or 8 mm depending on the application and study design. Although spatial smoothing enhances the SNR, recent reports suggest that it might affect and bias the results of resting-state fMRI studies that perform functional network analysis (Alakörkkö et al., 2017).



FIGURE 2.12: Effects of spatial smoothing using different values of the Full Width at Half Maximum (FWHM)

3.7 Temporal Filtering

Resting-state and task-activated fMRI signals contain low frequencies of no interest that arise from scanner drifts, coil interference, and slow vascular/metabolic oscillations (< 0.008 Hz) as well as high frequencies of no interest related to physiological fluctuations such as breathing and heartbeat (0.3-1.0 Hz). Therefore, studies usually apply **temporal filtering** in the form of low-, high-, or band-pass filters to attenuate the effect of signals with these frequencies within the raw fMRI data (Figure **??**). For instance, rsfMRI studies are mostly interested in low-frequency fluctuations (< 0.1 Hz). Therefore, band-pass filtering is commonly applied to attenuate frequencies outside the range [0.01-0.1 Hz (or 0.08 Hz)]. However, recent studies have shown that meaningful information might be present at high frequencies, suggesting that high-pass filtering may be more advantageous than low-pass and band-pass filters (Boubela et al., 2013). In task-based fMRI studies, the range of the frequencies of interest is dependent on the timing of the presented stimulus, and many fMRI experiments include randomly presented stimuli (i.e., event-related designs), also suggesting the presence of meaningful information at high frequencies. Therefore, most task-based fMRI and some rsfMRI studies avoid low-pass filtering and instead use high-pass filtering only.



FIGURE 2.13: Effects of temporal filtering using a highpass (top) and a lowpass (bottom) filters. Figure reproduced from MRIQuestions

3.8 Nuisance Regression

In the past two decades, there has been a proliferation of techniques tailored towards mitigating motion and physiological artifacts in BOLD-fMRI data that are not accounted for by simple realignments and filtering. One of the most popular strategies has been confound or **nuisance regression**. Nuisance regression entails removing signals believed to be of non-neuronal origin from the BOLD-fMRI data using multiple linear regression. As a result of this regression, the data become orthogonal (i.e., residualized) with respect to confounding variables and hence can be used with confidence in subsequent analyses with more confidence. The signals commonly removed in nuisance regression often include combinations of the six motion parameters, tissue-specific signals from white matter (WM) and cerebrospinal fluid (CSF), the average (or global) signal, the first order derivatives of these, their quadratic terms, quadratic terms of the derivatives, linear trends, regressors corresponding to volumes heavily affected by motion (i.e., "spike regressors"), physiological recordings of cardiac pulsations and respiration (i.e., RETROICOR), principal components derived from noise regions of interest (i.e., aCompCor and tCompCor) (Behzadi et al., 2007), and signals identified as noise via data-driven techniques based on independent component analysis (ICA-FIX or ICA-AROMA; Pruim et al., 2015). However, even slightly different combinations of nuisance variables can alter the results and lead to different interpretations and conclusions (Ciric et al., 2017).

This plurality in choices and the inherent flexibility involved in nuisance regression have motivated many studies to evaluate the effect of different combinations of regressors according to a number of benchmarks (see Ciric et al. (2017), Friston et al. (1996), Jo et al. (2010), and Parkes et al. (2018) for reviews). Nevertheless, there is still no gold-standard solution for nuisance removal, and controversy still exists regarding the benefits and perils of adjusting for certain variables, most notably, the global signal (Murphy and Fox, 2017; Li et al., 2019). Moreover, recent reports have demonstrated that subject-level nuisance regression is not sufficient to effectively attenuate noise, and hence group-level adjustments are also recommended (Power et al., 2012; Power et al., 2014). Finally, its has been shown that nuisance regression steps and temporal filtering operations are not commutative, and the order in which they are performed is important as they basically project the data onto a subspace, whereby it becomes orthogonal to nuisance variables and to signals of no interest (Lindquist et al., 2019). So, performing many projections in series can reintroduce nuisance signals that have been removed in previous projections. Thus, it is now highly recommended to combine those steps into a single linear filter/regression step or to sequentially orthogonalize the nuisance variables with respect to temporal filters and each other prior to nuisance regression (Hallquist, Hwang, and Luna, 2013; Lindquist et al., 2019).

3.9 Despiking

Recent studies have demonstrated that small head movements (i.e., micromovements) in the range of (0.5-1 mm) can induce systematic biases in the analysis of fMRI data (Power et al., 2012). These studies suggest that standard methods of nuisance regression and volume realignment cannot remove the more subtle effects of micromovements, particularly in groups of children and patients, where larger spike-like head movements are prevalent and often correlate with age or disease symptom severity (Patel et al., 2014). Different **despiking** approaches have been proposed to attenuate the subtle effects of head motion not accounted for by standard preprocessing techniques. The most straightforward method is scrubbing or volume censoring. Scrubbing is often performed on the basis of the frame-to-frame or framewise displacement (FD) to identify and censor volumes heavily affected by head motion (Power et al., 2014). This is achieved by simply removing those volumes and temporally interpolating the missing data or by including them as "spike regressors" in the nuisance regression step. Another approach, commonly referred to as "Time Despike", identifies spikes at the voxel level as supra-threshold deviations from the local median of absolute deviations, or MAD, calculated at each time point using two to six neighbouring time points on either side, and compresses any detected spikes to the level of the MAD (Patel et al., 2014). Finally, a recently introduced data-driven approach, known as "Wavelet Despike", identifies non-stationary events caused by micromovements, using a wavelet-based approach. Wavelet-based approaches, such as wavelet transforms, enable the analysis of the properties of complex timeseries in the wavelet domain (Daubechies, 1992), provide multi-frequency information about signals, and are effective at detecting transient phenomena, such as sudden spikes (Patel et al., 2014). The wavelet despike algorithm identifies non-stationary events across different frequencies as chains of maximal or minimal wavelet coefficients, despikes them from voxel timeseries without distorting the overall temporal structure, and recovers the denoised fMRI signals (Patel et al., 2014). Despiking can be performed earlier in the preprocessing pipeline to account for the effects of large spikes prior to coregistration and normalization. However, Patel et al. (2014) demonstrated that applying wavelet despike before nuisance regression and directly after spatial smoothing produced better results.

4 Functional Connectivity

It has long been thought that behavior is not merely encoded in discrete brain regions, but rather emerges from the functional interactions between regions. The fMRI community has grasped this concept from the beginnings and have since focused on inferring brain-behavior relationships through functional connectivity (Buckner, Krienen, and Yeo, 2013). The notion behind this connectivity approach is that areas are presumed to be coupled or participate in the same network if their activities consistently co-vary together to some extent. A great effort has been dedicated in the last two decades to investigate functional connectivity, and the exponential growth in findings has been supported by an influx of analysis methods and applications from across the natural, social, and information sciences, providing neuroscientists with the means to explore and begin to understand the relation between inter-regional functional coupling and behavior across different populations (Van Den Heuvel and Pol, 2010). Although FC is a measure of undirected communication, it is fairly simple enjoying more analytical flexibility than directed measures (e.g., effective connectivity) that often require neurobiological and biophysical modelling with many different parameter and a clear hypothesis. In the following subsections, we broadly summarize the most commonly used FC analysis methods, highlighting the values and limitations of each. We first introduce some of the statistical dependency measures used for quantifying FC and then we move on to summarize seed-based, ROI-based, and graph analysis approaches. For more elaborate descriptions and comparisons of mentioned and unmentioned methodological choices, the reader is referred to specialized reviews, such as Bastos and Schoffelen (2016), Bijsterbosch, Smith, and Beckmann (2017), Toga (2015), and most recently Pervaiz et al. (2020). Note that, although FC analysis is more abundant in rsfMRI than in task-based studies, the methods and measures explained below are generally compatible with and have been used in both study designs. Therefore, unless explicitly mentioned, FC is referred to in the general sense.

4.1 Measures of Functional Connectivity

A considerable amount of work and methods have been directed to evaluating and characterising FC observed using fMRI. However, despite the varying levels of complexity between the different methods and measures, the ultimate goal is to quantify the level of synchronization between pairs of simultaneously recorded BOLD timeseries extracted from distributed brain regions. For this purpose, metrics of statistical dependence have been used, with **Pearson's product-moment correla**tion being perhaps the most commonly used measure (Friston, 2011). In principle, any generic measure for estimating dependence can be used to quantify FC, but Pearson's correlation is credited for its simplicity and versatility (Fornito, Zalesky, and Bullmore, 2016). Denoted by r or ρ , Pearson's correlation is defined as the linear covariance of two timeseries divided by the product of their standard deviations (Equation 2.1, Figure 2.14). It is bounded between -1 and 1; a high, positive correlation coefficient close to 1 indicates strong in-phase coupling; a correlation coefficient close to zero indicates no relation; and a negative correlation coefficient close to -1 indicates anti-coupling or strongly out-of-phase relation between signals. Both positive and negative correlation inform us about the nature of interactions between brain systems: positive values imply integration, whereas negative values imply antagonism or segregation. However, the nature of negative correlations is still debated, and there is little consensus on how to handle and interpret negative FC in the brain. Due to this ambiguity, many studies choose to discard negativelyweighted FC and only analyze positively-weighted FC (see Hallquist and Hillary (2018) for a recent review). Pearson's correlation is defined as:

$$\operatorname{Corr}(x,y) = \frac{\operatorname{Cov}(x,y)}{\sqrt{\operatorname{Var}(x) \times \operatorname{Var}(y)}}$$
(2.1)

where cov(x,y) is the covariance between the timeseries and var(x) and var(y) represent the variance in each timeseries, respectively.

Computing Pearson's correlation entails different assumptions about the data, such as linear relationships among variables, normality of variables, and independent observations (Kirch, 2008). Faithfully presuming the first two conditions are

met (however this may not be the case), fMRI-FC studies often apply Fisher's rto-z transformation (z = arctanh(r)) to the correlation coefficients in order to stabilize their variance and make valid statistical inferences, provided that the third assumption is also met in this case (Afyouni, Smith, and Nichols, 2019). However, the variance of the correlation coefficients and their standardized z-scores counterparts heavily depends on the independence of successive timepoints in any given timeseries (Bartlett, 1946). However, observation independence is not a property of BOLD timeseries. In general, the hemodynamic response function (HRF) is sluggish and has an overall cycle of about 12-15 seconds, while typical TRs in an fMRI experiment are around 2 seconds. This causes the BOLD timeseries to exhibit serial autocorrelation (i.e., dependent observations), which can in turn inflate the variance of correlation coefficients and reduce the effective number of degrees of freedom (EDF) in the data (Afyouni, Smith, and Nichols, 2019), violating the third assumption of Pearson's correlation. Ignoring this variance inflation and the overall reduction in EDF will inflate the z-scores as well and produce an excess of false positives when testing hypotheses, which leads to misleading conclusions (Afyouni, Smith, and Nichols, 2019). However, to solve the issue of autocorrelation and ensure valid statistical inference, ad hoc solutions have been proposed, such as Bartlett's method of dividing arctanh(r) by a data-driven deflated-EDF (Afyouni, Smith, and Nichols, 2019; Bartlett, 1946), prewhitening of BOLD timeseries (Bright, Tench, and Murphy, 2017), computing Pearson's correlation in the wavelet domain instead of the time domain (Patel and Bullmore, 2016), and the recently introduced, more robust extension of Bartlett's method: the cross-EDF or xDF (Afyouni, Smith, and Nichols, 2019). For recent reviews and comparisons of methods that adjust for serial autocorrelation in fMRI-FC analysis, see Afyouni, Smith, and Nichols (2019) and Olszowy et al. (2019).

An important limitation of Pearson's correlation is its sensitivity to "third party" effects. That is, two BOLD timeseries can exhibit a strong positive correlation, even in the absence of a direct connection between the regions involved (see Li et al. (2009) for a review). This can arise because the activity of one or both regions correlates with the activity of a third, intermediary region. However, if only direct connections are of interest, the conditional or **partial correlation** between a pair of



FIGURE 2.14: Pearson's correlation coefficient among the BOLD timeseries of three different brain regions. This figure illustrates the differences between positive, negligible, and negative FC.

BOLD timeseries can be computed by statistically removing the effect of timeseries of all remaining brain regions via multiple regression or covariance matrix inversion. Partial correlation provides a sparser representation of whole-brain FC than "full" correlation and can better relate to the underlying direct structural connectivity (Huang and Ding, 2016). However, a considerable increase in the number of regions of interest (ROIs), given the noisy BOLD timeseries with finite length, may lead to a rank deficient covariance structure in the data (Varoquaux and Craddock, 2013). That is, the covariance matrix may be ill-conditioned and possibly un-invertible, rendering the computation of partial correlations computationally challenging and unreliable (Ledoit and Wolf, 2004). To circumvent this issue and counteract the "curse of dimensionality" without losing data, regularized estimation of full and partial correlations have been suggested. These measures are estimated using covariance penalization (shrinkage) methods including, among others, the Ledoit–Wolf estimator (Ledoit and Wolf, 2004), Tikhonov regularization (L2regularization; Golub, Hansen, and O'Leary, 1999), least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996), and Sparse Graphical Gaussian Models

(SGGMs) (Ng et al., 2013), that provide reliable estimates of the covariance structure in high-dimensional data (Brier et al., 2015; Varoquaux and Craddock, 2013). So far, however, there is no clear consensus on whether FC have to be based on full (i.e., marginal) or partial (i.e., conditional) correlations. Nonetheless, both measures reveal fundamentally different properties of brain FC, and hence the choice highly depends on the question in hand, sample size, and the number of brain regions of interest (see Vico Fallani et al. (2014), Hallquist and Hillary (2018), Pervaiz et al. (2019), and Varoquaux and Craddock (2013) for reviews on the topic).

A second limitation of Pearson's correlation is that it is defined at "zero lag", making it highly sensitive to the shape and delays of the HRF, which can vary between brain regions and individuals. For example, older adults have a delayed hemodynamic response compared with younger adults or children (D'Esposito, Deouell, and Gazzaley, 2003), and the parameters of an individual's HRF, such as onset delay, time to reach peak, and width can vary across regions due to vascular differences (Sun, Miller, and D'Esposito, 2004). In other words, two regions might be functionally connected, but due to a time delay between their activity profiles, Pearson's correlation may not be the optimal choice to quantify this interdependence. Moreover, BOLD timeseries have fractal scaling properties meaning that they exhibit details and meaningful structure on multiple temporal and spectral scales (Achard et al., 2006). A popular measure that is invariant to inter-regional and inter-individual differences in the HRF, insensitive to the autocorrelation of BOLD timeseries, and is well-suited for the analysis of fractal timeseries is the spectral/wavelet coherence (Sun, Miller, and D'Esposito, 2004), also known as the magnitude-squared coherence. Coherence measures the level of synchrony, in the spectral or wavelet (i.e., time-frequency) domains, between a pair of BOLD timeseries that have been filtered within specific narrow-band frequency bandwidths and subjected to a Fourier or a wavelet transform (Fornito, Zalesky, and Bullmore, 2016; Sun, Miller, and D'Esposito, 2004). Mathematically, coherence is the spectral (or wavelet) domain analog of the time domain cross-correlation coefficient. That is, its squared value quantifies the amount of variance in one timeseries that can be explained by the other timeseries in the frequency domain, in analogy to the squared correlation (i.e., r^2) in the time domain. Moreover, unlike the time-domain

correlation coefficient, coherence is a function of frequency with values bounded between 0 and 1. These values indicate how well timeseries a timeseries x corresponds to timeseries y within a certain frequency bandwidth, with 0 indicating no correspondence and 1 indicating total correspondence. This simplifies the analysis and interpretation of FC at the expense of losing the distinction between different types of functional interactions (i.e., coupling vs. anti-coupling). The spectral coherence between two timeseries x and y at a given frequency f is defined as:

$$\operatorname{Coh}_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$
(2.2)

where Pxy(f) is the cross-power spectral density of x and y, and Pxx(f) and Pyy(f) are the power spectral densities of x and y at frequency *f*, respectively. For reviews and studies that use spectral and wavelet coherence (and wavelet-domain cross-correlation) in FC analysis, see Achard et al. (2006), Achard and Bullmore (2007), Gardner (1992), Grinsted, Moore, and Jevrejeva (2004), and Sun, Miller, and D'Esposito (2004).

Correlation and coherence efficiently capture linear dependencies, but they are not suitable for measuring inter-regional relationships when regional activity might exhibit non-linear properties. To overcome this issue, measures that are sensitive to both linear and non-linear relationships, most notably mutual information (Salvador et al., 2007; Wang et al., 2015), have been used to quantify FC. Mutual information, or MI, has been adapted from information theory and determines how different the joint distribution of the pair of variable (e.g., BOLD timeseries) is to the product of their marginal distributions (Equation ??). MI is measured in bits and can be thought of as an indicator of uncertainty about one random variable given knowledge of another variable. The higher the value of MI the larger the reduction in uncertainty and vice versa, whereas a value closer to zero indicates that the variables are mutually exclusive. Thus, MI is believed to provide a more clear physical meaning about the strength of FC than correlation or coherence (Wang et al., 2015). So far, however, the advantages and disadvantages of using MI as a measure of fMRI-FC have not been extensively characterized, and its applications remain limited compared with linear measures of FC. For more information on the use of MI

in fMRI, see Chai et al. (2009), Salvador et al. (2007), Wang et al. (2015), and Zhang et al. (2018).

4.2 Methods of Analysis

Seed-based Analysis

Seed-based FC analysis is a popular model-based technique that provides straightforward and easy-to-interpret results with few constraints on the definition of brain regions. Specifically, seed-based FC analysis involves selecting a voxel or a ROI as a "seed", extracting the corresponding BOLD timeseries, and using Pearson's correlation or any other measure of dependency to estimate the FC between the seed and every other voxel in the brain, in an exploratory fashion. The output is a wholebrain FC map demonstrating the level of synchronization between the seed's activity and the activity of the rest of the brain (Figure 2.15). The primary advantage of seed-based FC over other methods is that it provides a direct answer to a welldefined hypothesis and helps in making direct inferences of brain-behavior relationships. However, this method requires a prior knowledge or hypothesis-driven selection of the seed region, which imposes restrictions on the measurement of FC and cannot be generalized to test systems-level hypotheses and construct connectomic representations of brain function (Cole, Smith, and Beckmann, 2010). Thus, the disadvantage of seed-based FC analysis is its dependence on the user's choice, which makes it highly vulnerable to statistical bias if the choice has not been driven by a clear and sound hypothesis. Finally, apart from whole-brain FC analysis, seedbased approaches are useful for quantifying regional FC profiles (i.e., within region FC) using measures such the amplitude of low frequency fluctuations (ALFF), fractional amplitude of low frequency fluctuations (fALFF), and regional homogeneity (ReHo). The latter is based on an assumption that a given voxel or seed is temporally correlated its neighboring voxels and, thus, reflects information about the regional integration of information processing. See Cole, Smith, and Beckmann (2010), Lv et al. (2018), and Smitha et al. (2017) for comprehensive reviews on seedbased FC analysis.



FIGURE 2.15: Seed-based FC analysis for resting-state (top) and task-based fMRI (bottom) investigations. The heat maps (right) represent correlation scores between every brain voxel and a predefined seed region (left). Figure adapted from Toga (2015), with permission.

ROI-to-ROI and Independent Components Analyses

To explore and understand connectome-wide associations, several methods have been introduced that enable the exploration of whole-brain FC patterns without the need of defining an *a priori* seed region. There is a multitude of methods to quantify FC between brain ROIs covering the whole brain. However, despite the apparent technical differences between methods, there is a common workflow that goes as follows (Figure 2.16: (i) A set of brain ROIs is defined according to pre-established brain atlases based on anatomical or functional priors or directly derived from the data at hand; (ii) BOLD timeseries are extracted for each ROI; (iii) FC values between pairs of ROIs are finally estimated using any measure of statistical dependence (e.g., correlation or coherence) and conveniently arranged in a square matrix of size *N*, where N is the total number of ROIs. From there, further analysis can be conducted to relate pairwise connections to behavior, estimate meaningful metrics that describe the network organization of the brain, and compare FC matrices between healthy and diseased populations.

Defining ROIs is conventionally known as **parcellation**. Many studies use anatomically-defined brain parcellations that are based on brain morphometry (e.g., Brodmann areas) or cytoarchitecture with little to no functional relevance, whereas



FIGURE 2.16: A typical ROI-based FC analysis workflow. The first step is defining ROIs based on either functional or anatomical atlases. Then, the BOLD timeseries are extracted from each ROI and a functional connectivity matrix is constructed by computing a measure of dependency between the timeseries. Thresholding can be done after that *but it is an optional step. A graph can be constructed from which meaningful measures of network topology can be estimated. Figure adapted from Uehara et al. (2014).

other studies prefer functionally homogeneous and spatially constrained ROIs derived from the data or pre-established by previous studies using other data. The heterogeneity in choices makes it difficult to combine results across studies and draw consistent conclusions. As a result, there is a very active field of research focused on defining whole-brain parcellations that best fit the brain's functional organization. Nonetheless, there is still no clear consensus as to which is the best parcellation or method to derive parcellations. Additionally, it is a common practice to use the same parcellation across all study subjects, which ignores the interindividual variability and within-individual variability as a function of cognitive state (Salehi et al., 2020; Yaakub et al., 2020). This is often the case of anatomical parcellations, such as the Automated Anatomical Labelling (AAL) atlas that is based on single-subject images (Tzourio-Mazoyer et al., 2002). Although some anatomical structures support a direct mapping to specific functions (e.g., the primary visual areas), anatomical definitions of brain regions are mostly independent of the explored function and may merge functionally distinct neuronal clusters (Yaakub et al., 2020). Additionally, individual variations in FC estimated from a single functional parcellation, with the underlying assumption that parcels are invariant in size or location across subjects, has been shown to be almost entirely explained by the spatial configuration of regions rather than actual differences in FC strength (Bijsterbosch et al., 2018; Salehi et al., 2020). Recently, methods for precision functional mapping of subject-specific ROIs have been proposed and used across different studies (Gordon et al., 2017; Laumann et al., 2015; Marek et al., 2018), but they require highly-sampled BOLD-fMRI data acquired across several hours (Gordon et al., 2017). However, in case such data are not readily available, group-level ROIs that are adapted to functional data are more suitable for modelling brain FC than those adapted to histological or cytoarchitectonic boundaries.

Functional parcellations can be derived directly from the data at hand (Beckmann et al., 2005), defined according to pre-established and cross-validated functional atlases (Gordon et al., 2016; Schaefer et al., 2017; Yeo et al., 2011), or created via large-scale meta-analyses of previous resting-state and task-based fMRI studies (Power et al., 2011). Popular data-driven approaches include, but are not limited to, spatial independent components analysis (sICA; Beckmann et al., 2005), temporal ICA (Calhoun and Adali, 2012), dictionary learning (Varoquaux et al., 2011), principal components analysis (PCA) (Kiviniemi et al., 2009), mixture models (Lashkari et al., 2012), k-means clustering (Kahnt et al., 2012; Yeo et al., 2011), hierarchical clustering (Michel et al., 2012), spectral clustering (Craddock et al., 2012), and gradientbased methods (Gordon et al., 2016; Schaefer et al., 2017). Here, only sICA (in particular group sICA) is described owing to its straightforward and prevalent use across many studies.

Group spatial ICA (GICA), is an unsupervised data-driven method that can be used to derive spatial maps of functional networks in the brain, extract useful biomarkers for brain disorders, and denoise BOLD-fMRI data (Beckmann et al., 2005; Calhoun, Liu, and Adalı, 2009; Pruim et al., 2015). GICA is based on blindsource separation, which traditionally attempts to discover hidden sources that underlie observed data (Calhoun, Liu, and Adalı, 2009). A classical example that is often used to explain blind source separation is the "cocktail party problem", which describes a situation where an individual attending a cocktail party is unable to segregate the different voice sources that have interfered to create the overall mixture of noise, and attempts to do so by focusing on each source independently, while ignoring other sources (Cherry, 1953).



FIGURE 2.17: A typical output of a group independent components analysis (GICA) showing a set of large-scale brain networks. A-B default mode networks; C-D left and right frontoparietal executive control networks; E-F visual networks; G-H attention/salience networks; I-J sensorimotor networks.

In fMRI, GICA assumes that the observed BOLD data is a mixture of independent sets of data that originate from unobserved (hidden) sources, which can either be functional networks/regions or noise of non-neuronal origin (Beckmann et al., 2005). In a typical GICA setting, the observed fMRI data are temporally concatenated across all subjects and organized into an *N* matrix, where N is the total number of timepoints and M is the total number of voxels (i.e., observed spatial features) in the brain. This high-dimensional matrix undergoes an initial two-stage dimensionality reduction step using PCA; first a subject level PCA followed by a grouplevel PCA on the components (PCs) from all the subjects (Calhoun and Adali, 2012). PCA linearly transforms the high-dimensional, correlated voxel data into a smaller number of uncorrelated principal directions (features or components) that explain a maximal amount of variance in the data, that is to say, a small set of variables that capture most information of the data in a low-dimensional space, first at the subjectlevel then at the group-level. GICA then attempts to factor the PCA-reduced data into a product of a set of timecourses and a set of maximally independent spatial activation maps (i.e., unobserved spatial features, Figure 2.17), known as independent components (ICs), that can be classified as either functional brain networks or noise based on direct visual inspection or spectral properties (Calhoun and Adali, 2012). The number of ICs of interest is a free parameter, which can be either theoretically/heuristically determined or estimated using data-driven techniques (Beckmann et al., 2005). Many algorithms and toolbox softwares have been developed to analyze and decompose fMRI data using GICA. The most commonly used algorithms are Infomax and FastIC, which can be found across different software packages, such as the GIFT toolbox http://mialab.mrn.org/software/gift/.

A major issue in the application of GICA is the instability of the estimated ICs across different runs of the algorithm. This is because most GICA algorithms have a stochastic nature and may converge to different local minima across different runs. To solve this issue, different model-selection tools have been developed and can be used to perform multiple runs of GICA, visualize the different outcomes, and collect the most stable set of group-level ICs from different runs of GICA according to special criteria and quality metrics. The most commonly used tool for this purpose is the ICASSO, which is implemented in the GIFT toolbox software (Himberg, Hyvärinen, and Esposito, 2004; Li, Adalı, and Calhoun, 2007). In ICASSO, absolute correlation coefficients are computed among the spatial maps of ICs across different runs and employed as a measure of similarity. Then, a group-average agglomeration strategy can be used to group similar ICs across runs in clusters attributed to the same independent source. The most stable and reliable estimates of ICs are automatically obtained by retrieving the centrotype of each cluster, i.e., the estimate that

is most similar to the others in each cluster (Li, Adalı, and Calhoun, 2007). ICASSO also offers quantitative evaluations of the "compactness" of each cluster of IC estimates. A compactness index close to 1 indicates that the estimation is stable and highly consistent, i.e., highly similar components are estimated at each run of the ICA algorithm. For further technical information regarding GICA and ICASSO, the reader is referred to Calhoun and Adali (2012), Cole, Smith, and Beckmann (2010), Erhardt et al. (2011), Himberg, Hyvärinen, and Esposito (2004), and Li, Adalı, and Calhoun (2007).

Finally, in rsfMRI, RSNs are commonly computed at the group level, providing no subject-level information necessary to make statistical inferences at a later stage of analysis. However, a common need for brain FC analysis is to first perform a GICA, and then, for each subject, estimate a version of each RSN and a corresponding BOLD timeseries. This is usually achieved using the dual regression technique (Nickerson et al., 2017). In the framework of dual regression, each group-level spatial map (i.e., RSN) is regressed onto each subject's BOLD-fMRI data to extract the corresponding subject-specific BOLD timeseries. Then, the extracted timeseries are regressed onto the same BOLD-fMRI data to obtain the subject-specific set of RSNs (Beckmann et al., 2005; Nickerson et al., 2017). In recent years, more advanced extensions of GICA and dual regression have been developed and can provide better estimations of subject-specific RSNs. The most notable method is the group information guided ICA (GIG-ICA), which utilizes the group-level ICs, obtained from a preceding GICA, as guidance to compute subject-specific ICs and timeseries using a multi-objective optimization strategy that can also be applied to fMRI data not included in the computation of the initial group ICs (Du and Fan, 2013). GIG-ICA simultaneously optimizes the independence among individual networks of each subject and the dependence of networks across subjects, providing a convenient balance between the group model (fixed networks) and the individual subject specificity of the estimated networks (Salman et al., 2019).
Graph Analysis

The brain is perhaps the most complex network known to humans (Fornito, Zalesky, and Bullmore, 2016). On the microscale, a human brain is made up of a hundred billion neurons connected by an extraordinary mesh of 100 trillion synapses. Moving up to the mesoscale, a brain is made up of hundreds and thousands of interacting functional units connected by anatomical fibers and/or functional connectivity. At the macroscale, the brain's functional network organization is summarized by a handful of large-scale networks each subserving a functional domain and interacting with other networks to generate complex behaviors. Indeed, if perturbed at any scale, the brain can exhibit many uncertainties and non-linear events that are difficult to predict and evaluate without prior knowledge of all details of the network (Betzel and Bassett, 2017). However, it is an overwhelmingly difficult, yet very important, task to fathom how the brain is organized in every detail, how functional networks give rise to complex cognition and behavior, and how are they altered brain disorders. In this context, graph theory has been introduced to network neuroscience research to afford neuroscientists an opportunity to characterize, estimate, and simulate the minute details of brain networks using fairly simple, yet highly effective models.

Graph theory is a branch of mathematics concerned with the analysis of complex relationships among the components of an interconnected system (Bassett and Bullmore, 2017; Fornito, Zalesky, and Bullmore, 2016). A graph is a simple model made up of a set of **nodes** linked by a set of **edges** (Wilson, 1986). In the context of the brain, a graph is made up of brain regions/networks/voxels (nodes) connected by structural connections or by FC weights (edges). For examples, the AAL atlas (Tzourio-Mazoyer et al., 2002), which contains 116 anatomical ROIs, or the Power-264 atlas (Power et al., 2011), which contains 264 functional ROIs, can be used to define the nodes, whereas Pearson's correlation can be used to compute pairwise FC weights, which define the edges.

As an optional preprocessing step, brain FC graph may undergo thresholding and binarization to remove spurious connections and further simplify the analysis. In FC graph analysis, thresholding is the process of removing FC weights that fall below a prespecified cut-off threshold (Heuvel et al., 2017). In some cases, thresholding can be followed by binarization, whereby surviving FC weights are set to 1 and those that do not survive are set to 0. A thresholding strategy in a typical FC graph analysis can use an **absolute threshold** or a **proportional threshold** depending on the research question, although other types of thresholds exist, such as probabilistic thresholds (Váša, Bullmore, and Patel, 2018). Nonetheless, it has been shown that different types of thresholding may lead to different results or even bias group comparisons, especially when comparing healthy controls to cohorts characterized by low overall FC, such as schizophrenia (Heuvel et al., 2017). An alternative approach is to use fully-weighted networks suited for computing graph measures that are robust to spurious FC weights, discarding the need for thresholding in the first place (Heuvel et al., 2017). The advantage of fully-weighted networks is that they better reflect the small-world properties of brain networks, and that edges with lower weights actually have less impact on the overall network organization compared with stronger connections (Schwarz and McGonigle, 2011; Heuvel et al., 2017). Moreover, studies have shown that weak connections are organized precisely as predicted by the theory of cost-efficient information transfer in the brain (Gallos, Sigman, and Makse, 2012). That is, a network in which strong links form largeworld fractal communities, weak links form shortcuts between them, establishing a small-world global brain network that supports cross-module interactions and hence efficient flow of information (Gallos, Makse, and Sigman, 2012). Yet, whether using thresholded or fully-weighted graphs depends on the research question and the data at hand. For more information and comprehensive reviews on thresholding, see Fornito, Zalesky, and Bullmore (2016), Jalili (2016), Van Wijk, Stam, and Daffertshofer (2010), and Heuvel et al. (2017) and Váša, Bullmore, and Patel (2018).

Whether using fully-weighted or thresholded graphs, the topological features of the FC graph can be characterized by meaningful measures, such as degree, strength, degree distribution, hubs, and rich clubs, to name a few. The **degree** is the total number of connections (in binary graphs) a given node has with the rest of the network. A similar measure is the **strength**, defined as the total sum of FC weights of a given node with all other nodes in the network. Another related concept is the **degree distribution** that describes how the degrees and strengths of all nodes in a network are distributed and allows researchers to determine whether a network contains centralized **hubs** that connect to many nodes (Van Den Heuvel and Sporns, 2011). One of the major discoveries that emerged from graph theory is that the nodes of many real-world networks—including the brain—do not connect randomly nor uniformly, but rather follow a **power-law** or a scale-free distribution (Fornito, Zalesky, and Bullmore, 2016). Power-law distributions describe graphs that have a topological core-periphery organization with nodes of the core having a very large number of connections and those in the periphery having fewer connections. The core nodes are often called **hubs** that serve central roles in the network and facilitate efficient cross-network information transmission through short-range connections (Achard et al., 2006; Van Den Heuvel and Sporns, 2011). Hubs that are also strongly connected to one another form what is known as a **rich club** organization (Van Den Heuvel and Sporns, 2011).

Another important set of second-level graph measures include, among others, the clustering coefficient, characteristic path length, small-worldness, efficiency, and modularity. The clustering coefficient measures the tendency of nodes in a graph to cluster together in groups of strongly connected nodes called communities. Two versions of this measure exist: the global and the local clustering coefficients. The global clustering coefficient gives an indication of the overall connectedness of the entire network, whereas the local clustering coefficient gives an indication of the tendency of single nodes to join clusters or communities. The characteristic path length, also known as the average shortest path length, is a measure of the average number of connections between all pairs of nodes, and can be an indicator of the cost-efficiency of a network. That is, larger values of the characteristic path length indicate less cost-efficiency (i.e., long distances and high "wiring" cost), whereas smaller values indicate greater cost-efficiency (i.e., short distances and low "wiring" cost). The interplay between the characteristic path length and the clustering coefficient determines the small-worldness of a network (Bassett and Bullmore, 2017). Small-worldness is formally defined as the ratio of the clustering coefficient to the average shortest path length; a small-world network is characterized by large clustering coefficient and small characteristic path length, reflecting efficient information transmission with minimal wiring costs. In this context, a measure of global and local **efficiency** can be computed from the reciprocal of the characteristic path length. Global efficiency quantifies the exchange of information across the whole network, whereas local efficiency is computed a the level of nodes and can quantify the capacity of information transfer through each node.



FIGURE 2.18: Schematic representation of three important graph measures: clustering coefficient, modularity, and path length.

Finally, **modularity** is an important property of many real-world networks and describes the strength of segregation of networks into modules over several topological scales in a Russian doll-like organization (Fornito, Zalesky, and Bullmore, 2016). The brain's modular structure reflects regularities in its wiring diagram, such that brain regions or neurons that are highly connected and putatively perform common functions are grouped together (Crossley et al., 2013). Moreover, the brain's community structure spans hierarchical organizational scales, ranging from microscale communities at the neuronal level to mesoscale communities of functionally-specialized regions to macroscale communities associated with a broader range of brain functions (Betzel and Bassett, 2017). Essentially, hierarchical, modular networks have small-world properties such as dense, short-range intramodular connections and sparse, long-range inter-modular connections. In this sense, the intrinsic functional organization of the human brain manifests as hierarchically organized RSNs, has small-world properties, and is remarkably flexible, exhibiting a fractal community structure that transcends multiple levels of space, time, and topology (Betzel and Bassett, 2017). For comprehensive reviews on all mentioned and unmentioned graph measures and on the use of graph analysis in neuroscience, in general, see Achard et al. (2006), Bassett and Bullmore (2017), Bondy, Murty, et al. (1976), Bullmore and Sporns (2009), Vico Fallani et al. (2014), and Fornito, Zalesky, and Bullmore (2016) and Sporns (2018).

5 Dynamic Functional Connectivity

5.1 Introduction

The emergence of large-scale networks during both resting-state and task performance, as measured by fMRI, is a widely studied phenomenon (Damoiseaux et al., 2006; Chang and Glover, 2010). Such networks reflect the average, stable functional organization of the brain and are derived from a scanning period of 5 minutes or more based on an implicit assumption that FC over this duration is relatively stationary (Calhoun et al., 2014). That is, FC has been considered "static" in a sense that all time points in a fMRI scan are taken to produce a single measure of average FC strength (Fong et al., 2019). However, the brain is an inherently dynamic system that rapidly integrates, coordinates, and responds to multiple internal and external stimuli at fast timescales in order to complete complex tasks and achieve goals (Hutchison et al., 2013). Therefore, the "static" perspective of FC, although informative, is a narrow view of brain functioning, precluding the harnessing of information embedded in very fast variations in FC and necessary to answer fundamental questions about the function and dysfunction of the human brain (Zalesky et al., 2014). In this context, different approaches have been recently developed to study the brain as a time-varying or "dynamic" interconnected system with a functional network organization that reconfigures over timescales shorter than a standard task (Bassett et al., 2011; Braun et al., 2015; Gonzalez-Castillo and Bandettini, 2018; Sakoğlu et al., 2010; Shine et al., 2016) or resting-state fMRI session (Allen et al., 2014; Chang and Glover, 2010; Damaraju et al., 2014; Liégeois et al., 2019; Zalesky et al., 2014).

The interest in dynamical inter-dependence between neurons (i.e., the modulation of activity in one brain region caused by the activity in other regions) actually goes back to the mid 20th century. Dynamical approaches have been applied to analyze neural systems across different spatial scales including ion channels, single cell firing, microscopic field potentials, and scalp EEG data (see Breakspear (2004) for a comprehensive review on this topic). This has been supported by the ability of these modalities to directly measure, with sub-second resolution, the fast oscillations in neuronal signalling subserving diverse perceptual and cognitive operations. However, this type of analysis did not attract the interest of the fMRI community at first, mostly because BOLD signals are much slower than the underlying neuronal signals—placing a fundamental limit on the temporal resolution of fMRI-FC measures—and are highly sensitive to external noise such as breathing, cardiac pulsations, and head movements (Lurie et al., 2020). Instead, fMRI studies have focused on FC changes as a function of age (Supekar, Musen, and Menon, 2009), visual state (Bianciardi et al., 2009), awareness (e.g., sleep, sedation, anesthesia) (Beason-Held, Kraut, and Resnick, 2009), and cognitive state (e.g., different task conditions and resting state) (Fransson, 2006). In the latter case, studies have shown that attention (Fransson, 2006) and learning (Sun et al., 2007) can induce changes in coordinated BOLD fluctuations throughout the performance of cognitive task and in subsequent rsfMRI scans. Yet, these findings have been based on measuring FC variations across different scanning sessions and not on measures of short-term variations within a single session.

In the early 2010s, Chang and Glover (2010) have undertaken one of two earliest fMRI experiments to examine the within-session temporal variations in restingstate FC, happening at timescales of a few seconds between two brain networks thought to be dominantly and consistently "anti-correlated" across time. Particularly, using a joint time-frequency analysis and sliding window analysis, Chang and Glover (2010) have examined the variability of resting-state FC between the posterior cingulate cortex (PCC), a primary node of the DMN, and regions of the antagonist (or "anti-correlated") executive control network (ECN) as well as other regions of the DMN itself. This has been motivated by preceding observations that the magnitude of negative FC between the two networks is much weaker and much less consistent than within-network positive FC across scanning sessions, especially when global signal regression, which introduces artificial negative correlations, is not performed (Chang and Glover, 2009; Shehzad et al., 2009; Murphy et al., 2009). Moreover, because the resting brain may exhibit varying levels of attention, mind wandering, and arousal, Chang and Glover (2010) have also hypothesized that the FC within and between networks may vary across the duration of a scan. Indeed, it was found that the coherence and phase coupling between the BOLD timeseries of the PCC and regions of the ECN are variable in time and frequency, and that the two networks exhibit temporally-localized epochs of strong negative connectivity interspersed by transient periods of weakly coordinated co-activation, which explains the weak negative correlation between them. Additionally, using **sliding window** analysis to segment the BOLD timeseries into non-overlapping time intervals, Chang and Glover (2010) have found that more regions exhibit a variable FC profile with the PCC, including the so called "task-positive" regions known to be part of the attention and salience networks. These early findings, among others (Sakoğlu et al., 2010), have marked the beginning of a new era in fMRI-FC research, which takes into account that FC may exhibit dynamic changes at timescales of few seconds during an fMRI scan.

Many studies of TVFC have focused on quantifying the temporal variability (i.e., standard deviation from the mean) in FC between pairs of brain regions within narrow time intervals or frequency bandwidths (Chang and Glover, 2010), which, during resting state, is believed to underlie a general readiness for these regions to reconfigure their connectivity profile when environmental conditions change (Chang and Glover, 2010). Other studies have used extensions of traditional graph theory analysis to TVFC, such as multilayer network approaches (Mucha et al., 2010), which attempt to quantify dynamic reconfigurations in modular structures. This modular flexibility have been associated with a broad range of cognitive and pathophysiological factors, including learning (Bassett et al., 2011), cognitive flexibility (Braun et al., 2015), emotion regulation (Betzel et al., 2017), and schizophrenia (Gifford et al., 2020), to name a few. However, the vast majority of studies have focused on extracting a set of patterns that capture the main modes of whole-brain TVFC. Perhaps the main and most controversial finding in this context is that whole-brain functional network organization transitions back and forth between a set of quasistationary and recurring (possibly overlapping) states that are stable for a short period time (Cabral, Kringelbach, and Deco, 2017; Calhoun et al., 2014; Heitmann and Breakspear, 2018; Lurie et al., 2020; Vidaurre et al., 2018). These states are

characterized by unique FC patterns, spatial co-activation patterns, probabilities of occurrence and transition, and subject-specific timecourse profiles that reflect the most likely sequence of state "visits" for each subject (Vidaurre et al., 2018). The spatiotemporal properties of the states are thought to reflect nonrandom reorganization of functional interactions that give rise to stable RSNs at extended periods and might encode information not captured by the time-averaged measures of FC (Cabral, Kringelbach, and Deco, 2017; Calhoun et al., 2014; Vidaurre, Smith, and Woolrich, 2017). Moreover, studies have found that FC states at rest are largely reproducible across individuals and datasets, even when data are collected from multiple scanning sites and different populations (Abrol et al., 2017; Lurie et al., 2020). As a natural consequence of these findings, the term **chronnectome** has been coined by Calhoun et al. (2014), as the time-varying analog of the connectome, to describe a focus on identifying time-varying, but recurring, patterns of functional coupling among brain regions.

While there is clear evidence that the time-varying properties of brain FC derived using electrophysiological recording modalities (e.g., EEG and MEG) relate to momentarily recurring cognitive states, whether or not fMRI's TVFC reflects actual shifts in communication modes between neuronal populations is still, somehow, controversial (Lurie et al., 2020). However, there is a growing literature on taskrelated reconfiguration in FC at short timescales, which has shown that measures of TVFC can predict performance on tasks both inside and outside the scanner (Douw et al., 2016; Gonzalez-Castillo and Bandettini, 2018; Liégeois et al., 2019; Shine et al., 2016) and infer an individual's emotional experience during the performance of a task (Tobia et al. (2017); see Shine and Poldrack (2018) for a review on the topic). Moreover, task-based TVFC methods have been used to identify functional network reconfigurations associated with different task conditions (Braun et al., 2015; Quinn et al., 2018) and learning (Bassett et al., 2011). However, in the absence of external tasks and any ground truth during resting state, discerning whether the intrinsic TVFC has a cognitive and behavioral relevance has not been a straightforward task (Vidaurre et al., 2019). In addition, the relatively low temporal SNR and the major sources of noise in rsfMRI, including system-related instabilities, head motion, and

physiological fluctuations have led to considerable skepticism regarding the presence neuronal origins for TVFC (Lurie et al., 2020). However, spontaneous fluctuations are a hallmark of neuronal signalling and studies have found strong associations between intrinsic TVFC and simultaneously recorded electrophysiological data (Chang et al., 2013; Lindquist et al., 2014) and neuronal calcium signals in mice (Matsui, Murakami, and Ohki, 2019) as well as cognitive performance (Cabral et al., 2017), attention (Fong et al., 2019), creativity (Li et al., 2017), personality traits (Liégeois et al., 2019; Vidaurre et al., 2019), and a growing number of brain disorders (Engels et al., 2018; Gifford et al., 2020; Harlalka et al., 2019; Rashid et al., 2014), suggesting a neuronal origin for resting-state TVFC measured by fMRI (see Zhang et al. (2016) for a review on the topic).

Over the past decade, the number of methods used in the analysis of TVFC have grown exponentially in terms of volume and complexity. Although a review of all existing methods along with their merits and pitfalls is an absolute necessity, it is beyond the capacity of this general overview chapter to cover all methods in detail. However, in the following subsections, some of the most commonly used analysis methods in the TVFC literature are described along with their merits and pitfalls. However, for comprehensive reviews and technical details of the different methods used in TVFC analysis, the reader is referred to these key reviews (Betzel and Bassett, 2017; Cabral, Kringelbach, and Deco, 2017; Calhoun et al., 2014; Filippi et al., 2019; Hindriks et al., 2016; Hutchison et al., 2013; Laumann et al., 2017; Lurie et al., 2020; Preti, Bolton, and Ville, 2017; Shine et al., 2015)

5.2 Methods of Analysis

Sliding Window Analysis

The sliding window analysis is perhaps the most commonly used and straightforward method in the study of TVFC (Allen et al., 2014; Damaraju et al., 2014; Hindriks et al., 2016; Calhoun et al., 2014). It is analogous to a moving average function, whereby it computes a succession of pairwise FC matrices over overlapping or nonoverlapping segments of the BOLD timeseries extracted from brain ROIs or voxels (Figure 2.19B). For example, given two simultaneously recorded BOLD timeseries



A Identification of intrinsic connectivity networks (ICNs)

FIGURE 2.19: A standard sliding window and clustering approach to identify time-varying patterns of functional connectivity from fMRI Data. (A) Identifying resting-state networks and extracting BOLD timeseries using group independent components analysis. (B) Performing a sliding window analysis (left) for every subject and applying k-means clustering (right) across all windowed FC matrices from all subjects to extract FC states. Figure reproduced from Calhoun et al. (2014), with permission.

with 400 timepoints each, we compute Pearson's correlation (or any other measure of dependency) between them within a window that covers the first 20 timepoints. Then, we move or "slide" this window by one timepoint such that it covers timepoints 2 through 21, and compute the pairwise correlation coefficient again. We repeat this procedure until the 400 timepoints have been covered by 370 overlapping windows. Performing this procedure across all pairs of ROIs or voxels yields a timeseries of FC matrices from which several descriptors of TVFC can be computed, such as the mean and variability (i.e., standard deviation) or time-dependent graph measures (Bassett et al., 2011; Braun et al., 2015; Gifford et al., 2020; Sizemore and Bassett, 2017). Moreover, clustering techniques, such as k-means clustering, can be applied to the upper triangular part of the windowed FC matrices obtained in a group of subjects to estimate a set of FC states and quantify their temporal properties (Figure 2.19).

Although the use of sliding window correlations is both simple and versatile, it entails some caveats. Importantly, the results of sliding window analysis are highly

sensitive to the different choices of parameters, such as window shape, length, and choice of FC metric (Hindriks et al., 2016). In the case of window shape, most studies use a rectangular window that assigns the same weight to all underlying timepoints, potentially increasing the sensitivity of Pearson's correlation, for instance, to noise and outliers, especially at the sharp edges of the window (Mokhtari et al., 2019). To limit the effect of sharp edges and noise, some studies have proposed using exponentially weighted (Lindquist et al., 2014; Zalesky et al., 2014) or tapered windows (Allen et al., 2014; Rashid et al., 2014). On one hand, the exponentially weighted window, also known as the exponentially weighted moving average (EWMA), applies declining weights to past observations in the timeseries and places the strongest weights on recent observations, and after each "sliding" step, timepoints are gradually down-weighted by a factor λ , before eventually being removed from further computations of FC. This has been previously proposed for financial timeseries data (Lindquist et al., 2014). On the other hand, tapered windows deal exclusively with edge effects by gradually down-weighing timepoints that are far from the middle section of the window according a bell curve shape such that the timepoints at the edges are ultimately assigned zero weights, thereby limiting the effect of sharp edges. This tapered window can be created by convolving a rectangular window spanning, for example, 20 timepoints with a Gaussian kernel with a standard deviation σ =3 TRs (Allen et al., 2014; Rashid et al., 2014; Mokhtari et al., 2019).

Another important parameter is the **window length** that needs to be carefully set in order to obtain reliable estimates of TVFC (Hindriks et al., 2016). Although there is still no systematic account nor a theoretical support for any particular window length in the analysis of TVFC, empirically grounded rules-of-thumb that guide the choice of an appropriate length are widely used in the literature. One simple approach is to use varying window lengths, for example 15, 20, 30, 60, and 120 timepoints, and assess the findings' robustness to different choices. However, it has been reported that even small changes in window length can systematically alter the results (Leonardi and Van De Ville, 2015), and thus including many choices of window lengths as a validation analysis may complicate the interpretation of findings. In an effort to ease the perplexing window length issue, Leonardi and Van De Ville (2015) have proposed a rule-of-thumb for choosing a minimal window length depending on the choice of highpass temporal filtering applied to the BOLD timeseries. For example, if the BOLD timeseries are bandpass filtered in the range [0.01Hz-0.1Hz], then the minimal window duration needs to be at least $\frac{1}{0.01} = 100$ seconds. This is because the sliding window acts as a non-uniform lowpass filter in the frequency domain, and spurious fluctuations in windowed correlations have been observed when the window length is too short with respect to the underlying frequency components (Leonardi and Van De Ville, 2015). However, the authors have recommended the use of 30-60 seconds windows to capture reliable TVFC and discriminate FC states, provided that a proper highpass filter that matches the chosen window length is used.

Another commonly used rule-of-thumb requires the characterization of the extent of information that certain lengths can provide (Telesford et al., 2016). For instance, short windows (<30 seconds) can capture faster variations in FC, but at the cost of introducing spurious measures due to the small number of timepoints. In contrast, long windows (\approx 75 seconds to 150 seconds) have been shown to provide more reliable measures of windowed FC and better discriminate the dynamic roles of different brain regions in a temporal core-periphery organization (Telesford et al., 2016), but at the expense of not capturing fast changes in FC (Leonardi and Van De Ville, 2015). Therefore, it has been suggested that 30-60 seconds windows is a reasonable middle-ground choice , although some studies have suggested the use of window lengths of 120 or 240 s (Savva, Mitsis, and Matsopoulos, 2019).

Finally, the choice of **FC measure** is also critical for TVFC analysis. The most frequently used measures are the Pearson's correlation (Allen et al., 2014; Gifford et al., 2020; Lurie et al., 2020; Rashid et al., 2014; Savva, Mitsis, and Matsopoulos, 2019) and wavelet transform coherence (Bassett et al., 2011; Betzel et al., 2017; Braun et al., 2015; Braun et al., 2016; Chang and Glover, 2010; Patel and Bullmore, 2016), whereas other measures have been sparsely used, such as Spearman's rank correlation and mutual information (Hindriks et al., 2016; Preti, Bolton, and Ville, 2017; Savva, Mitsis, and Matsopoulos, 2019; Vergara et al., 2017). So far, however, there is no clear consensus on the "best" set of sliding window parameters and the choice

remains highly dependent on the research question and the data at hand. For a reviews and studies on sliding window analysis, see Hindriks et al. (2016), Savva, Mitsis, and Matsopoulos (2019), and Thompson et al. (2018).

Instantaneous Connectivity Analysis

The use of use sliding window analysis, as mentioned earlier, imposes restrictions on the length and shape of the window, which might compromise the temporal resolution and lead to varying conclusions across studies (Hindriks et al., 2016). As a response, some studies have recently shown that it is possible to reliably maximise the temporal resolution by using instantaneous measures of brain FC (i.e., at each single timepoint), most notably **instantaneous phase synchronization** (Glerean et al., 2012) and **multiplication of temporal derivatives** (MTD) (Shine et al., 2015). Similarly to sliding window analysis, the output of these two methods is a timeseries of FC matrices that can be used for estimating FC states via clustering Cabral et al. (2017) or for computing time-varying graph measures (Pedersen et al., 2018).

Instantaneous phase synchronization (IPS), also known as instantaneous phase coherence, is widely used in physics to study the behavior of weakly-coupled oscillators (Rosenblum, Pikovsky, and Kurths, 1996). The main idea behind IPS is to estimate the magnitude of "phase-locking" between a pair of timeseries by first separating their amplitude information from their phase information, the latter of which can be used to estimate the difference in phase coupling at each timepoint. The first step is usually achieved by converting the original timeseries into their complex analytic versions using the Hilbert transform (see Le Van Quyen et al. (2001) for a review), whereas the second step is achieved by simply subtracting the phase timeseries and calculating the cosine of this difference at each timepoint as a measure of instantaneous FC. In the case of TVFC analysis with N ROIs, this procedure yields a timeseries of instantaneous FC matrices that can be conveniently arranged into an adjacency tensor of shape *T*, where T is the number of timepoints. The advantages of using IPS to compute TVFC are: (1) it is not affected by cross-subject variability in the amplitude of BOLD timeseries (i.e., the phase information are sufficient

to capture temporal variations in FC), and (2) it is a measure of non-linear dependency, which makes it more suitable for capturing non-linear variations in FC than Pearson's correlation that only captures linear properties (Glerean et al., 2012).

Like Pearson's correlation, IPS is bounded between -1 and 1, indicating maximal anti-coupling and maximal coupling, respectively (Cabral et al., 2017; Glerean et al., 2012). For instance, a phase difference equal to zero degrees at one timepoint indicates that the BOLD timeseries are maximally phase-locked, and hence IPS, calculated as the cosine of 0, is equal to 1. As the phase difference approaches 180 degrees (or π), the IPS approaches -1, indicating maximal anti-coupling or out-ofphase coherence. Using IPS to quantify TVFC bears some limitations. Importantly, like any instantaneous measure of dependency, IPS is susceptible to high-frequency noise fluctuations that are usually filtered out when using sliding window (Cabral et al., 2017). However, different approaches have been developed to overcome this issue, including bandpass filtering the BOLD timeseries within a narrow frequency band (e.g., 0.04–0.07 Hz) (Glerean et al., 2012) or by analyzing the dominant FC pattern captured by the leading eigenvector of each of IPS FC matrix, which conserves a sufficient amount of variance (Cabral et al., 2017). The latter technique is known as leading eigenvector instantaneous dynamic analysis, or LEiDA. For further reading and information on the use of IPS and LEiDA in TVFC analysis, see Cabral et al. (2017), Cabral, Kringelbach, and Deco (2017), Pedersen et al. (2018), and Glerean et al. (2012).

Multiplication of temporal derivatives (MTD) is a recently developed approach to estimate instantaneous FC during task performance (Shine et al., 2016) and resting-state (Shine, Koyejo, and Poldrack, 2016). Computing MTD is fairly simple: (1) the temporal derivatives of *N* BOLD timeseries of length *T* are calculated by subtracting each BOLD timeseries at timepoint t1 from itself at timepoint t, hence obtaining a timeseries (length=t-1) of temporal derivatives for each BOLD timeseries; (2) each temporal derivative timeseries is then normalized by dividing it by its standard deviation; and finally (3) the MTD is computed as the point-wise product of the standardized temporal derivatives timeseries of each pair of brain regions and conveniently transformed into an adjacency tensor of shape T - 1, for each subject (Shine et al., 2015). MTD is also susceptible to high-frequency noise. In this context, Shine et al. (2015) have suggested calculating a simple moving average of the MTD scores such that scores surrounding a point in time are averaged within a window of a pre-specified length. This solution yields similar results to those of the sliding window analysis. However, in MTD, short window lengths (<30 seconds) may be used with confidence, as simulations have shown that, when averaged, MTD are not as sensitive to low- and high-frequency noise as the sliding window correlation, are not adversely affected by the choice of highpass filter, and are robust to spurious effects of head motion (Shine et al., 2015). Besides, with short windows, MTD has shown higher sensitivity to fast changes in FC than sliding window, making it useful for capturing fast changes in cognitive state and for characterizing task-driven TVFC in event-related paradigms or studies of naturalistic stimuli (e.g., movie watching) (Shine et al., 2016). However, recent reports have suggested that MTD may be overly sensitive to very small, and possibly spurious, variations in FC, compromising its ability to detect meaningful variations in the absence of clear benchmarks, post hoc statistical assessments, and effective datacleaning strategies (Savva, Mitsis, and Matsopoulos, 2019).

Multilayer Network Analysis

The brain's network architecture is highly organized across multiple levels of granularity, from the microscale at the level of individual neurons to the macroscale at the level of entire brain systems that communicate at different timescales. Situated between these extremes is the mesoscale, which comprises medium-sized groups of highly connected nodes known as "communities" or "modules" and whose timevarying functional intra- and inter-connections can be captured with fMRI at short timescales (Betzel and Bassett, 2017).

Whether using sliding window analysis or instantaneous measures to quantify TVFC, the resulting FC matrices can be combined in a time-respecting manner to form an adjacency tensor that can be thought of as an ordinal **multilayer network** (Figure 2.20). The ordinal multilayer network configuration carries information about the evolution of the brain's network structure at short timescales, which can be quantified using measures derived from graph theory (Bassett et al., 2011; Betzel

and Bassett, 2017; Mucha et al., 2010). In fact, most of the "time-invariant" graph metrics can be extended to the time-resolved domain so that they can be easily computed on a multilayer network. These may include, small-worldness, characteristic path length, clustering coefficients, centrality, and rich clubs, to name a few (Kivelä et al., 2014; Sizemore and Bassett, 2017). However, the most commonly used multilayer network measure in TVFC analysis is that of **multilayer community detection**, which measures how the brain's functional modular organization varies across time-respecting layers (Betzel and Bassett, 2017; Braun et al., 2015; Mucha et al., 2010).

A straightforward approach to assess the time-varying modular organization is to identify communities in each layer, separately, and then compute a statistic that characterizes the changes in their size and membership (i.e., constituent nodes) across time (Betzel and Bassett, 2017). There are different criteria to define communities and many algorithms for detecting them including, the Louvain Method, non-negative matrix factorization, Newman's modularity, hidden Markov models, clustering and InfoMap (Betzel and Bassett, 2017; Newman, 2006). However, the most popular approach to quantify communities the iterative maximization of the modularity quality function, denoted *Q*, that directly compares the number (in case of binary graphs) or strength (in case of weighted graphs) of intra-community connections in each layer to what is be expected in a network of similar size and density having randomly distributed connections, also known as null network or model (Equation 2.3; see Fortunato and Hric (2016), Fornito, Zalesky, and Bullmore (2016), and Newman (2006) for reviews on the topic). The single-layer modularity quality function is defined as:

$$Q(\gamma) = \sum_{ij} \left[A_{ij} - \gamma P_{ij} \right] \delta(M_i, M_j)$$
(2.3)

where A_{ij} is the observed FC weight between nodes *i* and *j* in a single layer network, P_{ij} is the expected FC weight between nodes *i* and *j* in a random network (i.e., null model), Kronecker's $\delta(M_i, M_j) = 1$ if the community assignments M_i and M_j of nodes *i* and *j*, respectively, are the same and 0 otherwise. The parameter γ is the structural resolution parameter, which scales the relative importance of the null random weights against the actual FC weights. That is, large values of γ result in the detection of many small communities composed of a few nodes, whereas small values result in the detection of a few large communities composed of many nodes.

A major shortcoming of using single-layer methods in a multilayer setting is that the precise quantification of changes in module membership requires a map from a given module in one layer to itself in the next layer (Mucha et al., 2010). Such a map cannot be derived by methods applied to individual layers, separately, due to the heuristic nature of most well-known community detection algorithms (Clauset, Newman, and Moore (2004) and Fortunato (2010); see Fortunato and Hric (2016) for a review on the topic). That is to say, a module labeled as *module A* in one layer is not necessarily the same module labelled *A* in the next layer or the layer after. This can be presumably resolved using *ad hoc* and post-processing methods such as the Hungarian algorithm that optimally aligns similar modules across different layer (Munkres, 1957). Nevertheless, if there are strong topological similarities between different modules across layers this approach may fail, especially when analyzing large networks with a fractal topography (Khambhati et al., 2018).

A recent solution to this issue is using multilayer modularity maximization algorithms that represent powerful extensions of the single-layer methods (Bassett et al., 2011; Betzel and Bassett, 2017; Mucha et al., 2010). Importantly, the multilayer analog estimates the communities in all layers simultaneously in a self-contained manner, which resolves the problem of persistence or continuity of communities from one layer to the next (Betzel and Bassett, 2017). In particular, the algorithm treats the multilayer network as a combination of individual networks coupled through "artificial" ordinal links that connect node *i* in layer *s* to itself in the temporally adjacent layers s - 1 and s + 1 (Mucha et al., 2010). The multilayer modularity operates on the same idea as the single-layer version. That is, communities in each layer are defined by grouping nodes having connections stronger than expected in a random version of the network (Bassett et al., 2011). However, by adding inter-layer ordinal connections of weight, ω , besides grouping intra-layer nodes into communities, the multilayer modularity algorithm assigns nodes in different layers to modules, thereby accounting for the continuity of communities across layers (Equation 2.4; Betzel and Bassett, 2017). Yet, as ideal as it may seem, selecting values for ω and γ is not straightforward and there is still no theory-driven nor data-driven approach, at least in TVFC analysis, for selecting an optimal combination of parameters, although many heuristics exist, such as making a "grid search" and making a choice based on user-defined criteria (Gerraty et al., 2018). Therefore, in the absence of strong evidence to select one weighting scheme over another, in studies of TVFC at least, the free parameters are usually assigned the same *de facto* value, $\gamma = \omega = 1$, that can be heuristically varied over a narrow range to assess the robustness of findings (Bassett et al., 2011; Braun et al., 2015; Braun et al., 2016). Ideally, there needs to be a principled, data-driven approach for selecting the "correct" free parameters in modularity maximization methods. Which can be an interesting research topic in the future. The multilayer modularity quality function is defined as:

$$Q(\gamma,\omega) = \sum_{ijsr} \left[\left(A_{ijs} - \gamma P_{ijs} \right) \delta_{sr} + \omega \delta(ij) \right] \delta \left(M_{is}, M_{jr} \right).$$
(2.4)

where A_{ijs} represents the observed FC between node *i* and node *j* in layer *s*, P_{ijs} is the expected FC weight between nodes *i* and *j* in a random network (i.e., null model) derived from layer *s*, γ_s is the structural resolution parameter in layer *s*, $\omega_{j,r,s}$ is the inter-layer temporal resolution parameter or the connection strength between each node in layer *s* and itself in a subsequent layer *r*, $M_{i,s}$ and $M_{j,s}$ are the community assignments of nodes *i* and *j* in window *s*, respectively, and, finally, $\delta(M_{i,s}, M_{j,s})$ is equal to 1 when $M_{i,s}=M_{j,s}$ and equal to 0 otherwise.

The choice of the null model, *P*, is critical for multilayer modularity maximization. In the study of *temporal networks*, such as TVFC, the most commonly used null models employ random graphs derived from the observed adjacency matrices (Bassett et al., 2013). There are three types of null models usually adopted in the analysis of TVFC: connectional null models, nodal null models, and temporal null models, in which intra-network connections, inter-network connections, and order timepoints in an adjacency tensor are randomized to get a random (i.e., permuted) network, respectively (Bassett et al., 2011; Braun et al., 2015; Mucha et al., 2010).

In the first approach, the connections between nodes in each layer are randomly rearranged such that the total density of graph is preserved while the meaningful topographic properties are lost. The predominantly used model in this case is the Newman-Girvan null model (Newman, 2006) defined as:

$$P_{ijs} = \frac{k_{i,s}k_{j,s}}{2m_s} \tag{2.5}$$

where $k_{i,s}$ and $k_{j,s}$ are the strengths (or weighted degrees) of nodes *i* and *j* in a null-model version of layer *s*, respectively, and m_s is the density, or the total sum of weighted degrees, of the whole graph in layer *s*. The second approach requires linking a node in one layer, with a weight ω , to a randomly chosen node in the previous and next layers. Last, the construction of a temporal null model is based on randomly reordering the multilayer network layers in time. Then, the dynamic network measures computed using the observed multilayer community structure are statistically compared to those computed using the temporally permuted version (Bassett et al., 2011).

After determining the optimal community structure via multilayer modularity maximization or any other method with the appropriate null model, one can explore the architectural fluctuations and temporal excursions of each region from the "native" (i.e., time-averaged) network configuration using different network diagnostic measures. For example, flexibility (Figure 2.20C) has been largely used to quantify how frequently a brain region changes its community assignment from one layer to the next (Bassett et al., 2011; Betzel and Bassett, 2017; Mattar, Betzel, and Bassett, 2016). Increased flexibility has been associated with learning (Bassett et al., 2011), enhanced executive function (Braun et al., 2015), aging (Betzel et al., 2015), emotions (Betzel et al., 2017), and cognitive dysfunction in brain disorders (Braun et al., 2016; Gifford et al., 2020; Harlalka et al., 2019). Related measures are node promiscuity, cohesion, disjointness (Telesford et al., 2017). Promiscuity is the fraction of all the communities in which a node participates at least once across time (Papadopoulos et al., 2016). Cohesion measures the extent to which each node transitions mutually with other nodes between communities across layers, whereas disjointness measures the extent to which nodes move independently from between communities (Telesford et al., 2017). These two metrics are particularly informative for determining collective (or local) variations in the coordinated activity of brain regions thought to mark changes in general cognitive processing.



FIGURE 2.20: Construction of multilayer networks and computation of the flexibility. (A) BOLD timeseries are extracted from a pre-defined set of ROIs, (B) Dynamic FC matrices are computed either using sliding window or instantaneous measures of FC, (C) Multilayer modularity maximization algorithm uncovers community assignments across ordinal layers for all nodes. The temporal flexibility of each node in the network is then calculated as the average number of times it changes its community affiliation. Least flexible nodes tend to stay with the same community and rarely transitions to other communities, whereas most flexible nodes tend to change their community affiliation more often. This represents a temporal core-periphery organization, where inflexible nodes make up the core, while flexible node constitute the periphery. Figure reproduced from Mattar, Betzel, and Bassett (2016), with permission.



FIGURE 2.21: **(A)** The module allegiance matrix represents the proportion of time that any two brain regions are assigned to same community across layers. The warm block-like structure along the diagonal of the matrix suggests that nodes belonging to the same brain system tend to cluster together more often than with nodes outside the system across time. **(B)** The average allegiance value within the native system of the node represents the recruitment coefficient, whereas the average allegiance value outside the node's native system yields the integration coefficient. **(C)** Recruitment (top) and integration (bottom) for different brain regions in a study conducted by Chen et al. (2016). As seen from the figure, nearby regions (potentially belonging to the same brain system) tend to have very similar recruitment and integration profiles, suggesting the presence of system-level integration of information at short timescales. Figure reproduced from Mattar et al. (2015), with permission.

Another important set of measures can quantify the extent to which nodes participate in communities with nodes belonging to or outside their native system (Chen et al., 2016; Mattar et al., 2015). These measures require the computation of the average **module allegiance matrix** (sometimes called the temporal co-occurrence matrix; Figure 2.21A), for each study subject, in which each element measures the proportion of times that two brain regions have been assigned to the same community across layers (Chen et al., 2016; Gifford et al., 2020). The module allegiance matrix can be used to estimate the probability of brain nodes to show spatiotemporally diverse functional interactions with nodes outside their "native system" using a measure called **integration**. Conversely, the module allegiance matrix can be used to estimate the probability of brain nodes the probability of brain nodes to remain connected to nodes belonging to their time-averaged

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native community (Mattar et al., 2015). For comprehensive reviews and papers on the use of multilayer modularity analysis in TVFC, see Bassett et al. (2011), Betzel and Bassett (2017), Betzel et al. (2019), Chen et al. (2016), De Domenico (2017), Mattar et al. (2015), Mucha et al. (2010), Telesford et al. (2016), and Pedersen et al. (2018).

Hidden Markov Models

The sliding window analysis and related methods suffer from a number of limitations that may undermine and complicate the analysis of TVFC, potentially leading to false conclusions if not carefully accounted for (Hindriks et al., 2016). In particular, they need a careful pre-specification of the timescales (i.e., window length) within which reliable estimates of windowed FC can be computed. A recent alternative approach to sliding window analysis is the hidden Markov models (HMM), which belong to the class of probabilistic graphical modelling tools specifically designed for the analysis of sequential data (e.g., timeseries). HMM can be used to directly segment the observed BOLD timeseries into a set of states characterized by distinct FC configurations that reoccur over time, in a self-contained manner (Quinn et al., 2018). That is, the HMM method does not require a pre-specification of any window length (Quinn et al., 2018). Instead, the timescales of interest are inferred directly form the observed data (Quinn et al., 2018; Vidaurre, Smith, and Woolrich, 2017). Particularly, while sliding window analysis permit the estimation of FC within short data segments with a fixed length, the HMM decomposes the data efficiently by inferring adaptive "windows" or lifetimes for each state and then estimating FC patterns averaged across all visits to that state (Baker et al., 2014; Quinn et al., 2018; Vidaurre et al., 2018). This removes the necessity of prespecifying window length and the need for windows to be sufficiently long to get reliable estimates and short enough to capture fast changes in FC. Instead, the temporal properties of the states such as frequency of occurrence and dwell times are independent of the semi-arbitrary choices of window and thus become interesting properties in themselves, driven by variations in the BOLD timeseries rather than the researcher's choice of parameters.

The HMM has been used to flexibly characterize FC states across a range of data modalities and has been applied to an increasing number of conditions and datasets that include resting-state (Vidaurre, Smith, and Woolrich, 2017) and different task paradigms (Quinn et al., 2018). The findings highlight the ability of the HMM to represent behaviourally relevant dynamics at different data-specific and data-driven timescales not captured by fixed sliding window analysis (Quinn et al., 2018). This approach has been extended to explore the relationship between states and cognition in very large datasets (Vidaurre et al., 2018). For example, brain states inferred by applying the HMM on massive resting-state fMRI data from the Human Connectome Project have revealed a hierarchical temporal structure characterized by two "metastates" each comprised of a set of sub-states (Vidaurre, Smith, and Woolrich, 2017). One of these metastates has been shown to represent higher-order cognition, and the other represents the primary sensorimotor systems. Importantly, the metastates have been consistently detected across different datasets, with findings showing that their temporal properties at the subject-level (e.g., frequency of occurrence) are heritable and predictive of psychological and personality traits (Vidaurre et al., 2018; Vidaurre et al., 2019).

The HMM method is based on the principles of Markov chains and variational Bayesian inference (Vidaurre, Smith, and Woolrich, 2017). A Markov chain is a stochastic process describing systems that are presumed to transition between a set of observable states (e.g., weather) according to certain probabilistic rules. Importantly, in a Markov chain the probability of a state to occur at one timepoint depends only on the state of the previous timepoint. In other words, the states before the current state do not directly affect the transition to a future state. Markov chains are often modelled by a graph that includes a set of observed states connected by transition probabilities (see Gagniuc, 2017 for a textbook on Markov chains). Similarly to Markov chains, the hidden Markov models can be used to model dynamic systems that are postulated to transition between states, such as the human brain. However, unlike Markov chains, the states in HMM are *hidden*, and the algorithm attempts to uncover these states and estimate their properties from the observed timeseries using variational Bayesian inference. In this framework, the observed timeseries are believed to have been "emitted" by the occurrence of given state at

each timepoint. That is, each state that can be identified by the HMM is defined as an instantiation of a certain family of probability distributions known as observation models (or emission probabilities) that have "emitted" the observed timeseries data at the timepoints when a certain state is "active" (Figure 2.22). For example, multivariate Gaussian distributions have been widely-used as observational models when modelling FC dynamics in fMRI studies (Vidaurre, Smith, and Woolrich, 2017).

In TVFC analysis, the HMM method assumes that the BOLD timeseries are generated from joint multivariate Gaussian distributions each characterized by a mean vector and a covariance matrix (Vidaurre, Smith, and Woolrich, 2017). The HMM attempts to infer those parameters (i.e., mean and covariance) directly from the observed data using **variational Bayesian inference** (Baker et al., 2014; Ryali et al., 2016; Vidaurre et al., 2018). The mean vector encodes the average signal intensities of brain regions when a certain state is active and hence represents a transiently recurring spatial "co-activation" pattern in the brain. The covariance matrix, on the other hand, can be interpreted as a state-specific FC pattern encoding the patterns of connectivity when a certain state is active (Vidaurre et al., 2018). Moreover, the HMM yields a description of the temporal properties of the states, such as the state timecourses (i.e., the probability of each state to be active at each time point in a timeseries) and the transition probabilities (i.e., the probability to transition from one state to each of the other states).

HMM is usually performed at the group level and, more precisely, applied to the concatenated timeseries across all study subjects (Vidaurre et al., 2018). This means that the states mean vectors, covariance matrices, and transition probabilities are defined for the whole group. Only the state time courses are, however, subject-specific—that is, states can be active at different moments for each subject. A recent extension to the HMM is the **dual estimation**, which is analogous to the dual regression or GIG-ICA used in the framework of GICA (Vidaurre et al., 2019). In dual-estimation, the HMM is first applied at the group level and then re-applied to each subject's BOLD timeseries while employing the group-level estimates as prior information when updating and re-inferring the states for each subject (Vidaurre et al., 2019). This procedure yields an individualised estimation of the co-activation



FIGURE 2.22: (A) Each sample at each timepoint can described as one of a set of discrete hidden states denoted X_t . Each state has an observation model Y which characterizes the distributions of the observed data whilst state X is "active". (B) A simple example of a system with two interacting nodes moving through three HMM states (red, blue, and green states). The observation model for each node is shown in the line plots to the left. Each state has a distribution for each node describing the observed values whilst that state is "active". The timeseries to the right show the observed data for each node (e.g., BOLD timeseries). The values are color-coded according to which state is "active" at each time point. Note that at each point in time the observed values are drawn from the distribution of the appropriate observation for that sample. The bottom row shows the state timecourse

for this simple system. Figure reproduced from Quinn et al. (2018), with permission.

patterns and FC matrices, the latter of which can be used, for example, to test for associations between TVFC and behavior. Then, the subject-specific states can be used to re-compute the state timecourses and transition probabilities for each subject independently from the group estimates (Vidaurre et al., 2019). Thus, with HMM combined with dual estimation, subject-specific data-driven estimates of TVFC can be computed, bypassing the limits of the sliding window analysis.

A limitation of HMM algorithm is that it requires a large amount of data and, possibly, more than one fMRI scan per subject to yield richer and more robust results, which is computationally expensive, especially when analyzing massive datasets like the Human Connectome Project. However, stochastic variational Bayesian inference approaches have been proposed and can be applied to very large neuroimaging datasets in an iterative cost-efficient manner (Vidaurre et al., 2018). A second limitation of the HMM is that it requires that the number of states be specified a priori, similarly to traditional k-means clustering (Vidaurre, Smith, and Woolrich, 2017). However, as argued by Quinn et al. (2018), the objective of HMM is not to establish a "correct" number of states to describe state transitions in the data, but rather identify a number that provides a good description at a desired temporal granularity dependent on the question at hand, similarly to the choice of the number of components in GICA (Quinn et al., 2018). Finally, given the heuristic nature of variational Bayesian inference (i.e., sensitivity to initial starting points), the HMM may yield slightly different outcomes across different runs of the algorithm (Karapanagiotidis et al., 2018). However, this issue is amplified when the number of states and/or number of channels (i.e., brain regions) increase, exponentially inflating the number of parameters to be estimated (Baker et al., 2014). Thus, in order to get consistent results, a trade-off must be made between the desired temporal resolution (i.e., number of states), number brain regions of interest, the free energy index (an index of the goodness-of-fit of the model), and the stability of estimates across different runs (Karapanagiotidis et al., 2018). For comprehensive mathematical and technical details on the use of HMM in TVFC analysis, see Baker et al. (2014), Kottaram et al. (2019), Ou et al. (2015), Quinn et al. (2018), Rabiner and Juang (1986), Vidaurre et al. (2016), Vidaurre, Smith, and Woolrich (2017), and Vidaurre et al. (2018).

Statistical Testing with Null Models

The use of any of the abovementioned TVFC approaches generates different measures that should not be directly regarded as estimates of "true" TVFC (Miller et al., 2018). Given the finite number of timepoints and the numerous sources of noise present in the BOLD data, measures of TVFC, such as temporal variance or state transitions, are subject to statistical ambiguity (Hindriks et al., 2016). Therefore, a proper statistical framework needs to be adopted to determine whether the observed variations in FC can be characterized as significantly "dynamic" (Hindriks et al., 2016; Liegeois et al., 2017). So far, the most commonly used approach is to simulate surrogate data from the original timeseries or TVFC matrices that preserve the first-order statistics (i.e., mean and variance of the real timeseries) and other properties such as the time-averaged FC, power spectral density, and amplitude distribution (Zalesky and Breakspear, 2015). This data is considered "null" in the sense that it lacks any meaningful time-varying structure as the one presumed to exist in the fMRI data (Miller et al., 2018). The surrogate data can thus be used to formulate a null hypothesis that the observed measures of TVFC are not timevarying. Then, statistical tests can be performed to find evidence in support of or against this hypothesis and determine whether a TVFC metric is reflecting statistically significant temporal dynamics or is attributable to background noise and resampling variability (Miller et al., 2018).

The most popular frameworks to simulate surrogate data are phase randomization and multivariate autoregressive randomization (Liegeois et al., 2017; Miller et al., 2018; Savva, Mitsis, and Matsopoulos, 2019)). Phase randomization (PR) can be used to generate null data by performing a Discrete Fourier Transform (DFT) to each BOLD timeseries, adding a uniformly distributed random phase to each frequency component, and finally applying inverse DFT to recover the phase-randomized BOLD timeseries (Liegeois et al., 2017). Importantly, randomized phases are generated independently for each frequency components, but are uniform across all brain regions (Liegeois et al., 2017). In the ARR method, on the other hand, the BOLD timeseries at a given timepoint is assumed to be a linear combination of the values of previous timepoints (Chang and Glover, 2010; Liegeois et et al., 2010; Liegeois et al., 2017). al., 2017; Zalesky et al., 2014). In this framework, a multivariate *vector* of all BOLD timeseries is regressed on a lagged vector of the same timeseries, with the optimal lag determined using different criteria (Chang and Glover, 2010). Then, the coefficients of this regression are estimated using multivariate ordinary least squares and used in the generation of surrogate timeseries. Next, using bootstrapping, surrogate timeseries having the same ARR coefficients (i.e., same stationary relationship as the original timeseries) are generated. Yet, regardless of the method used, the generated surrogate data are assumed to be null in the sense that they are stationary, linear, and follow a Gaussian distribution (Liegeois et al., 2017).

After generating the surrogate datasets, the TVFC analysis applied to the original BOLD timeseries is repeated for each set of null data to construct an empirical distribution of the measure of interest (e.g., temporal variability). Then, hypothesis testing (one-tailed or two-tailed) can proceed by selecting an α^{th} percentile (e.g., 95%) at which the null hypothesis can be rejected. If an observed value falls outside the critical value, the null hypothesis can be rejected and the alternative hypothesis that the observed measure is an estimate of "true" TVFC can be accepted. However, since the surrogate data are linear, Gaussian, and stationary, the null hypothesis can be rejected due to non-linearity, non-Gaussianity, and/or non-stationarity, which does not permit a clear conclusion regarding the presence nor absence of non-stationary FC (Miller et al., 2018). That is, the observed FC data can be statistically stationary, but exhibit non-linearities, which may lead to a false rejection of the null hypothesis (Liegeois et al., 2017). Moreover, studies have shown that the notion of "stationarity" assessed using the PR and ARR models does not necessarily imply the absence of meaningful FC state transitions observed using HMM, which can reveal a set of "metastable" brain states (Liegeois et al., 2017; Vidaurre, Smith, and Woolrich, 2017). These major limitations of statistical testing in TVFC analysis have triggered debates on whether it is necessary to test for the "presence or absence" of TVFC (Miller et al., 2018). According to recent studies, given the dynamic nature of the human brain and strong associations between TVFC and electrophysiological recordings (Chang et al., 2013), the focus should not be on whether the dynamics exist or not, but rather on how they might manifest over different temporal, spatial, and topographical scales and how do they relate behavior (Miller et al., 2018). For reviews and key papers on null models in TVFC analysis, see Chang and Glover (2010), Hindriks et al. (2016), Laumann et al. (2017), Liegeois et al. (2017), Leonardi and Van De Ville (2015), Lurie et al. (2020), Miller et al. (2018), Savva, Mitsis, and Matsopoulos (2019), and Zalesky and Breakspear (2015).

6 Summary

In summary, we have seen that fMRI has revolutionized neuroscience in a relatively short period of time, tacitly mirroring the dominance of localizationist/reflexive ambitions in the early days, and later supporting an integrative theory of brain function that recognizes the importance of resting-state brain activity, which in fact reflects a "restless brain". These breakthroughs have opened new research lanes to understand the nature and behavioral relevance of the ongoing "stream of consciousness" in the human brain. Moreover, we have seen that the past two decades have witnessed an exponential growth in methods for analyzing fMRI data, enabling neuroscientists to continuously ameliorate models of the topological, spatial, and temporal intricacies that give rise to well-organized network organization and complex human behaviors. In this context, we have discussed the merits and pitfalls of some of the most-commonly used methods for analyzing FC at different temporal scales. Importantly, we have shown that time-averaged measures of FC do not capture the full extent of brain function and time-varying FC can complement traditional methods in capture more complex network interactions, with several caveats. In the years to come, as the fMRI community will likely continue to grow in volume and diversity, new analysis methods and refined models of the brain's functional organization are likely to advance at a much faster pace, promising to unlock more secrets of the brain's functions and dysfunctions, inform technological advances in artificial intelligence, and promote individualized treatments of brain disorders.

Part II

Practical Work

Chapter 3

Static and Dynamic Measures of

Cerebro-Cerebellar Functional

Connectivity are Associated with

Self-reported Measures of

Impulsivity: A Resting-State fMRI

Study

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Abstract

Converging evidence from human brain studies and research in animal models suggest a possible role for the cerebellum in regulating impulsivity—a multifaceted, complex trait broadly defined as the tendency to act without foresight and believed to be orchestrated by multiple cognitive processes. The cerebellum is postulated to be involved in the processes underlying trait impulsivity, such as executive control and reward, maintaining them around a homeostatic baseline. The cerebellum does so through extensive anatomical and functional connections with association regions in the brain such as the prefrontal cortex and basal ganglia. In this context, growing evidence from functional magnetic resonance imaging (fMRI) studies associates impairments in cerebro-cerebellar functional connectivity (FC) with several brain disorders in which impulsive symptomatology is a part of the disease pattern. However, most of the findings have been based on static FC that does not vary across the entire duration of the scan, an approach now regarded as simplistic. Moreover, the relation between cerebro-cerebellar FC and normal trait impulsivity, which might underlie a predisposition to psychopathology, remains unclear. Here, we hypothesized that individual differences in multiple facets of impulsivity could be encoded in broad patterns of information processing involving the cerebellum and emerging from dynamic functional interactions among multiple brain systems. We tested this hypothesis using a publicly available dataset comprising highly-sampled resting-state fMRI data acquired in a group of healthy young individuals (N=134, fMRI durationpprox1 hour per subject) and self-report questionnaires of impulsivity. We applied group independent components analysis (GICA), static FC analysis, and hidden Markov models (HMM) to the restingstate fMRI data. In particular, we identified distinct cerebral and cerebellar resting-state networks (RSNs), computed time-averaged or time-averaged FC matrices, and modeled whole-brain intrinsic activity as a dynamic sequence of recurring FC states. This methodology allowed us to compute the total strength and temporal variability in cerebro-cerebellar FC and evaluate them against self-reported measures of impulsivity. Results revealed that the behavioral approach and inhibition systems scales negatively correlated with the (static) strength of the FC between the cerebellum and two brain networks: a frontal salience network and the basal ganglia network, respectively. Moreover, we found compelling evidence linking lack of premeditation and sensation seeking traits to dynamic resting-state FC between the cerebellum and set of integrative brain networks that subtend hub regions subserving top-down cognitive control and bottom-up reward/saliency processes. These findings show the cerebro-cerebellar FC dynamics are behaviorally relevant, predicting individual differences in behavioral traits not captured by traditional static FC. Together, the findings highlight the utility of complementing static FC approaches with dynamic FC analyses in furthering our understanding of the behavioral repertoire of the cerebro-cerebellar system and the neurobiology of complex behaviors.

1 Introduction

There is strong evidence that links individual differences in normal behaviors and personality traits to the liability for a broad range of neuropsychiatric disorders, such as substance addiction, pathological gambling, depression, and anxiety (Davis et al., 2012; Eisenberg et al., 2001; Krueger and Markon, 2006). One such common and crosscutting trait is impulsivity, which involves initiating actions that are premature, poorly planned, and inappropriate to context (Davis et al., 2012; Krueger and Markon, 2006; Moeller et al., 2001). Impulsivity is a complex, multidimensional personality trait present to varying degrees in healthy individuals as well as diverse neuropsychiatric populations (Bakhshani, 2014), and can be assessed using behavioral tasks and self-report questionnaires that measure two broad cognitive processes: inhibitory control (or response inhibition) and reward sensitivity (or reward-delay impulsivity) (Jauregi, Kessler, and Hassel, 2018). Individual differences in these processes are believed to arise from genetic and neuronal origins that are not well understood (Khadka et al., 2014). Nonetheless, developing a comprehensive neurobiological understanding of impulsivity in healthy populations may help map the etiological risks for developing a certain psychopathology and, ultimately, inform treatment or prevention strategies (Davis et al., 2012). In this context, converging evidence from neuroscience and functional neuroimaging research suggests that the monoaminergic neurotransmitter, cortico-striatal and cortico-limbic systems mediate the different cognitive constructs related to impulsivity (Dalley, Everitt, and Robbins, 2011; Davis et al., 2012; Fineberg et al., 2014; Mitchell and Potenza, 2014; Somerville, Hare, and Casey, 2011). However, scattered but consistent findings from human brain studies and research in animal models have motivated recent hypotheses for the involvement of the cerebellum and cerebrocerebellar networks in impulsivity Miquel et al., 2019. In short, findings suggest that the cerebellum may regulate impulsive behavior through its interactions with the prefrontal cortex and the basal ganglia (see Miquel et al., 2019 for a recent review).

Originally thought of as a sensorimotor structure, the cerebellum is now known to be functionally diverse and involved higher-order cognitive processes (Strick, Dum, and Fiez, 2009; Buckner, 2013; Sokolov, Miall, and Ivry, 2017). In this context, converging evidence suggests that the cerebro-cerebellar circuitry may contribute to complex cognitive processes that underlie different forms of impulsive behavior (Miquel et al., 2019). Primarily, as established by neuroimaging, viral neuronal tracing, electro-stimulation, and optogenetics studies, the cerebellum appears to be closely-related to brain regions that subserve cognitive, affective, and reward-related processes including the prefrontal cortex, posterior parietal cortex, anterior cingulate cortex, insula, ventral tegmental area, thalamus, and basal ganglia (Caligiore et al., 2017; Carta et al., 2019; Moreno-Rius and Miquel, 2017; Strick, Dum, and Fiez, 2009). Moreover, early studies on the cerebellar role in cognition and emotion have reported that patients with posterolateral and midline cerebellar damage exhibit impairments in executive control and emotional regulation and show signs of impulsiveness and behavioral disinhibition (Schmahmann and Sherman, 1997). Furthermore, preclinical and neuroimaging studies have shown that cerebro-cerebellar dysconnectivity is common in brain disorders in which abnormal impulsive behavior is part of the disease pattern, such as substance addiction and attention deficit hyperactivity disorder (Zeeuw et al., 2013; Jung et al., 2014). These findings, among others, support a relation between cerebro-cerebellar dysfunction and impulsive-type behaviors in different patient populations (Miquel et al., 2019). However, the relation between cerebro-cerebellar functional coupling and impulsivity in healthy populations has not been characterized and remains largely unclear.

Impulsivity is influenced by multiple brain systems that overlap with a "multiple demand network" (Golchert et al., 2017) and it is likely that inter-individual differences in this complex trait are associated with global patterns of functional interactions and balanced resource sharing among distributed brain regions (Davis et al., 2012). In this context, the cerebellum is hypothesized to be involved in organizing the timing and accuracy of diverse streams of information arising from multiple brain regions by implementing forward internal models of the environment for prediction of potential outcomes and rapidly adjusting thoughts and actions according to context (Barton, 2012; Schmahmann, 2019). Hence, the cerebellum is likely to interact with cerebral cortical and subcortical regions at fast timescales to ensure smooth, coordinated information transmission and processing across the brain and maintain a homeostatic balance between top-down and bottom-up influences on behavior (Miquel et al., 2019; Schmahmann et al., 2019; Sokolov, Miall, and Ivry, 2017). This aspect of cerebro-cerebellar coupling may be embedded in the intrinsic network organization of the brain, which is classically evaluated using resting-state functional magnetic resonance imaging (rsfMRI) and encodes various behavioral aspects such as the integration of cognition and emotions, monitoring of external environment, and personality traits at different timescales (Liégeois et al., 2019). In this context, previous studies have effectively used rsfMRI FC analysis to uncover a hierarchical organizational principle in the cerebellar cortex and delineate cerebellar representations of most well-known cortical networks, including an expanded representations of executive control networks (Buckner et al., 2011; Guell et al., 2018; Marek et al., 2018).

So far, most of the rsfMRI literature related to the cerebellum has been based on time-averaged measures of FC across entire scanning sessions. However, considering the dynamic nature of the human brain and the continuously changing environmental conditions, the assumption that FC remains constant over an extended period of time is an over-simplification that obscures important behavioral information embedded at timescales shorter than the scan duration (Zalesky et al., 2014). Accordingly, several analysis approaches have been developed to explore the time-varying aspects of brain activity and connectivity (see Lurie et al., 2020; Preti, Bolton, and Ville, 2017 for recent reviews). This new approach to analyze FC has advanced our understanding of the temporal organization of functional interactions in the cerebral cortex and their cognitive and behavioral relevance (Liégeois et al., 2019). In this context, converging findings point to the presence of an ongoing and nonrandom reconfiguration of functional brain networks that predicts cognitive abilities, such as attention, learning, creativity, and cognitive flexibility, and exhibits alterations in brain disorders (Allen et al., 2014; Bassett et al., 2011; Calhoun et al., 2014; Chen et al., 2016; Damaraju et al., 2014; Rashid et al., 2014). Measures of dynamic FC are believed to complement and, in some cases, outperform measures of static (i.e., time-averaged) FC in explaining complex behaviors (Liégeois et al., 2019). However, joint information from both approaches has been shown to
explain more variance in behavior and cognition than either alone (Ramos-Nuñez et al., 2017; Liégeois et al., 2019). Nonetheless, little is known about the dynamics of cerebro-cerebellar functional networks and their cognitive and behavioral correlates, even though the cerebellum is known to interact with most, if not all, cerebral regions at different timescales in support of complex behaviors beyond the sensorimotor domain (Schmahmann, 2019). That being said, we believe that by exploring cerebro-cerebellar resting-state FC at different timescales, we may gain further insight into the functional repertoire of the cerebellum and the cerebro-cerebellar system.

In this study, we hypothesized that different temporal aspects of cerebrocerebellar resting-state FC could be associated with different constructs related to impulsivity. So, we sought to quantify static and dynamic FC between cerebellum and distinct cerebral networks involved in cognitive, affective, and rewardrelated processes and test for associations with cross-sectional differences in impulsivity. Toward these goals, we employed a publicly available dataset comprising highly-sampled rsfMRI data, acquired in group of healthy young individuals (N=134), and two widely-used self-report questionnaires that assess different facets of impulsivity, namely the UPPS-P impulsive behavior scale and the BIS/BAS. Importantly, we used four 15-minute rsfMRI runs per subject to enhance the temporal signal-to-noise ratio in the data, improve the identification of cerebral and cerebellar networks, and reliably model FC dynamics. Accordingly, we analyzed the rsfMRI data from all runs and subjects using group independent component analysis (GICA) to identify separate sets of cerebral and cerebellar RSNs that accounted for the functional heterogeneity present in both structures. Then, we modeled static cerebro-cerebellar FC by computing Pearson's correlation (full and partial) between the timeseries of all pairs of RSNs. This permitted the calculation of the time-averaged strength of cerebro-cerebellar FC over the entire scanning session. Moreover, to measure temporal variations in FC, we performed hidden Markov modelling (HMM) of whole-brain FC dynamics to estimate subject-specific FC "states" defined as transiently recurring patterns of connectivity in the brain (Vidaurre, Smith, and Woolrich, 2017; Vidaurre et al., 2018). By providing quantified descriptions of FC states and how they manifest at the level of individuals,

the HMM permitted the calculation of the temporal variability in FC between the cerebellum and distinct cerebral RSNs, such that the overall variations in cerebro-cerebellar FC could be driven by spontaneous fluctuations in mental state. Finally, we used multivariate general linear models to evaluate the association between cerebro-cerebellar resting-state FC and self-reported impulsivity.

2 Materials and Methods

2.1 Participants

A total of 134 healthy young participants (62 females, ages 20-40 years) from the Neuroanatomy and Connectivity (N&C) dataset, which is part of the Max Planck Institute-Leipzig Mind-Brain-Body (MPILMBB) database, were included in this study. At the time of inclusion, all participants were healthy with no signs of any serious neuropsychiatric or neurological condition, fulfilled the MRI safety requirements, and provided written informed consent prior to their participation (see Mendes et al., 2019 for more details). Originally, the fully preprocessed and denoised dataset included structural and functional MRI data and a battery of behavioral assessments from 188 participants. However, due to a gap in the age distribution, we excluded 26 subjects older than 55 years. Moreover, 28 subjects were excluded for missing imaging and/or behavioral data from source. Summary statistics of demographic and behavioral data are provided in **Table 3.1** in the results section.

2.2 Self-Reported Measures of Impulsivity

To assess inter-individual differences in different forms of impulsivity, we used individual scores obtained from two self-report questionnaires: the **UPPS-P impulsive behavior** scale and the **Behavioral Inhibition and Approach Systems** scale, widely known as BIS/BAS. On one hand, the UPPS-P impulsive behavior scale is designed to measure impulsive behavior across the five-factor model of personality: negative urgency, positive urgency, sensation seeking, lack of premeditation, and lack of perseverance (Whiteside and Lynam, 2001). High scores on the negative and positive urgency sub-scales indicate a higher tendency to act quickly under the effect of negative and positive emotions, respectively. A high score on the lack of perseverance sub-scale indicates an inability to remain focused on an arduous or boring task, whereas a high score on the lack of premeditation sub-scale indicates a higher tendency to behave rashly without prior thinking or consideration of consequences. Finally, a high score on the sensation seeking sub-scale indicates a higher tendency towards seeking novel and exciting experiences (Whiteside and Lynam, 2001). On the other hand, the BIS/BAS scales measure two general motivational systems argued by theorists to underlie behavior: a behavioral inhibition system (BIS) that regulates the sensitivity towards punishment, non-reward and negative outcomes, and a behavioral approach system (BAS) that regulates the sensitivity towards desirable cues and non-punishment (e.g., rewards). A high score on the BIS scale indicates an increased sensitivity to negative outcomes of anticipated actions and hence a higher tendency to control impulses/responses or restrain actions in advance (i.e., proactive inhibition), whereas a high score on the BAS scale indicates an increased sensitivity to rewarding activities and hence a higher tendency to engage in goal-directed, rewarding behaviors and, potentially, higher levels of reward-delay impulsivity. The BAS scale included in this study is the sum of three sub-scales: BAS drive, BAS fun seeking, and BAS reward responsiveness. Collectively, these scales offer a sufficient set of variables that assess different constructs of impulsivity, most importantly inhibitory control and reward sensitivity.

2.3 MRI Acquisition

The structural MRI and rsfMRI acquisition parameters are described in full detail in Mendes et al. (2019). In summary, the high resolution structural images were acquired using a 3D MP2RAGE sequence using the following parameters: voxel size = 1 mm isotropic, bandwidth = 240 Hz/Px, FOV = 256240176 mm, TR = 5000 ms, TE = 2.92 ms, TI1 = 700 ms, TI2 = 2500 ms, flip angle 1 = 4, flip angle 2 = 5, GRAPPA acceleration with iPAT factor 3 (32 reference lines), and pre-scan normalization. As for functional images, four resting-state fMRI scans were acquired for each individual in axial orientation using T2*-weighted gradient-echo echo planar imaging (GE-EPI) with multi-band acceleration. Sequences were identical across the four runs, with the exception of varying slice orientation and phase-encoding direction. The phase-encoding direction was anterior–posterior (AP) for runs 1 and 3, and posterior-anterior (PA) for runs 2 and 4. The complete set of parameters was set as follows: voxel size = 2.3 mm isotropic, FOV = 202 x 202 mm, imaging matrix = 88 x 88, 64 slices with 2.3 mm thickness, TR = 1400 ms, TE = 39.4 ms, flip angle = 69, echo spacing = 0.67 ms, bandwidth = 1776 Hz/Px, partial Fourier 7/8, no prescan normalization, multi-band acceleration factor = 4657 volumes, duration = 15 min 30 s per run. Individuals were instructed to remain awake, during the resting-state scan, with their eyes open and to fixate on a cross-hair.

2.4 Preprocessing

The preprocessing pipeline is described in full detail in Mendes et al. (2019) and fully preprocessed functional data were obtained from https://ftp.gwdg.de/pub/ misc/MPI-Leipzig_Mind-Brain-Body/derivatives/. In summary, the preprocessing steps included (1) removal of the first 5 volumes (\approx 7 seconds) from each of the four resting-state runs, (2) Rigid body alignment to the first volume using FSL-MCFLIRT to obtain transformation parameters for motion correction; (3) fieldmap unwarping using FSL-FLIRT and FSL-FUGUE to estimate transformation parameters for distortion correction (Jenkinson et al., 2012), (4) boundary-based registration (BBR) of the rsfMRI data to the same subject's structural scan via FreeSurfer-BBR to estimate transformation parameters for co-registration, (5) spatial normalization of structural scans to MNI152 2mm space using diffeomorphic non-linear registration as implemented in the ANTsSyN algorithm to estimate transformation parameters for spatial normalization (Avants et al., 2011) (6) applying all transformation parameters to each rsfMRI volume in the four resting state runs in one interpolation step (i.e., Lanczos interpolation); (7) inclusion of six motion parameters, their first-order derivatives, and motion outliers (frame-to-frame displacement>0.5 mm) from Nipype's *rapidart* algorithm as nuisance regressors in a general linear model (GLM) to clean the data from motion-induced artifacts, (8) the *aCompCor* method

to remove physiological noise from residual data from the previous denoising step (Behzadi et al., 2007), and (9) bandpass filtering [0.01 Hz—0.1 Hz].

2.5 Group Independent Components Analysis (GICA)

The preprocessed fMRI data from all subjects were analyzed using group independent component analysis (GICA) implemented in the GIFT toolbox software http://mialab.mrn.org/software/gift/. GICA decomposes the functional data into linear mixtures of spatially independent components (ICs) that exhibit unique time course profiles (Allen et al., 2014). To characterize cerebro-cerebellar FC, we decomposed the rsfMRI data from the cerebrum and cerebellum into two separate sets of ICs that reflected the functional network organization of both structures. By applying a "cerebellum-only" GICA approach (Dobromyslin et al., 2012), we were able to extract well-defined cerebellar networks and timeseries that are usually overpowered by signals of cortical and sub-cortical origins when performing a whole-brain GICA (Kipping et al., 2016). Cerebral and cerebellar GICA analyses are explained in detail in the following subsections.

Cerebellum-Only GICA

The first step of the "cerebellum-only" GICA was to isolate the cerebellum from the rest of the brain. To do so, we generated an average cerebellar mask in MNI152 2 mm space using the standard MNI152 cerebellum template from FSL and excluded all non-cerebellar voxels located outside the mask. Then, we concatenated, demeaned, and variance normalized the cerebellar functional data from all subjects and applied principal components analysis (PCA) to reduce the dimensionality of the data to 100 subject-level principal components (PCs, retaining > 99% of the variance in the data) and, subsequently, 25 group-level PCs. Then, the *Infomax* algorithm was applied to the 25 group-level PCs to estimate 25 group-level ICs. To ensure stable estimations of cerebellar components, we repeated the *Infomax* algorithm 20 times using ICASSO (implemented in the GIFT toolbox software) that automatically selected the most stable set of 25 cerebellar ICs. Finally, we used the group information guided ICA algorithm, or GIG-ICA, to estimate subject-specific

cerebellar ICs and timeseries (see (Du and Fan, 2013; Salman et al., 2019) for reviews on GIG-ICA).

The selected number of cerebellar ICs (i.e., 25 ICs) was in accordance with previous studies that identified between 7 and 20 functionally homogeneous cerebellar RSNs using different data-driven techniques (Buckner et al., 2011; Bernard et al., 2012; Kipping et al., 2016; Wang et al., 2016). However, since noise may still be present in the data even after preprocessing and denoising, we assumed a slightly higher number of ICs than the putative number of cerebellar RSNs to allow for better disentanglement of cerebellar signals from each other and from noise. In this context, ICs that exhibited spatial activation patterns near the grey matter/white matter/cerebro-spinal fluid borders and/or featured irregular and functionally irrelevant patterns were removed from the data and discarded as noise. In contrast, ICs that exhibited unilateral/bilateral spatial activation in the grey matter and had relevance to well-known cerebellar functional networks (Buckner et al., 2011) were retained as RSNs. The timeseries of cerebellar RSNs were standardized to have a zero mean and a unit variance for each subject in each resting-state run. Finally, all retained cerebellar RSNs were arranged into putative functional groups based on their anatomical and functional properties and in accordance with previous studies (Buckner et al., 2011).

Cerebral GICA

A similar approach to the cerebellum-only GICA was performed to extract cerebral RSNs and timeseries. First, we generated an average "cerebrum-only" mask in MNI152 2 mm space using a standard FSL MNI152 brain anatomical template and excluded all voxels residing outside the mask (Jenkinson et al., 2012). Concatenated, demeaned, and variance normalized cerebral functional data from all subjects and runs were analyzed using PCA to estimate 120 subject-level PCs (retaining > 99% of the variance of the data) and, subsequently, 30 group-level PCs. We performed 20 runs of the Infomax algorithm using ICASSO to estimate and automatically select the most stable set of 30 cerebral ICs. Note that performing GICA assuming 30 group-level ICs can reliably recover large-scale brain RSNs convenient for subsequent FC analyses in terms of complexity, dimensionality and interpretability. Subject-specific ICs and timeseries were estimated using GIG-ICA. Then, the ICs that exhibited spatial activation near the edges and in the white matter were removed from the data and discarded from subsequent analysis; the timeseries of the retained RSNs were standardized to have a zero mean and unit variance for each subject in each resting-state run. Finally, RSNs were arranged into putative functional groups based on their anatomical and functional properties and in accordance with previous studies (Yeo et al., 2011).

2.6 Functional Connectivity Analysis

Static Functional Connectivity

To estimate static FC matrices, we computed pairwise Pearson's full and partial correlation coefficients in each of the four resting-state runs using the Ledoit-Wolf estimator as implemented in the scikit-learn python package (Ledoit and Wolf, 2004; Abraham et al., 2014). The subject-level, full and partial correlation matrices were r-to-z transformed using Fisher's transformation to stabilize the variance of correlation coefficients and corrected for the effective number of degrees of freedom using Bartlett's method (Bartlett, 1946; Afyouni, Smith, and Nichols, 2019). This method controls for the effect of serial autocorrelation, in the timeseries, on the estimation of FC (see Afyouni, Smith, and Nichols, 2019 for a review). Then, for each subject and in each resting-state run, we extracted the cerebro-cerebellar FC sub-matrix and calculated the total *strength* of FC between distinct large-scale cerebral RSNs and the cerebellum as the sum of **positively-weighted** edges between them, given as:

$$S_i = \sum_{j=1}^{J} w_{ij}, \quad w_{ij} > 0$$
 (3.1)

where S_i is the total FC strength between cerebral RSN *i* and the cerebellum and w_{ij} is the weight of the edge linking cerebral RSN *i* and cerebellar RSN *j* such

that $w_{ij} > 0$. Negatively-weighted edges were discarded due to the lack of consensus and ambiguity concerning their nature, interpretation, and means of analysis (Hallquist and Hillary, 2018). More importantly, the meaning and importance of negative FC within the context of cerebro-cerebellar networks is not known and should be explored in future studies.

We were interested in computing FC using both Pearson's full and partial correlation to examine different types of functional interactions in the brain. Full (or marginal) correlation reflected both direct and indirect connections, whereas partial (or conditional) correlation reflected direct connections between pairs of brain regions after removing the effect of all other regions (Varoquaux and Craddock, 2013). This is informative for our study for two reasons. First, given that cerebrocerebellar structural networks form segregated closed-loops circuits (Habas, 2016), it is likely that distinct cerebellar functional modules directly connect to singular cerebral components rather than directly affecting large-scale complex processes (Sokolov, Miall, and Ivry, 2017). Partial correlation can reflect this aspect of cerebrocerebellar connectivity better than full correlation. Second, it is believed that the cerebellum and cerebro-cerebellar networks are fundamental components of largescale integrative brain systems that work together in conjunction in support of embodied cognition-the theory that holds that cognitive and affective functions are not independent from sensorimotor or "bodily" functions (Barton, 2012; Guell, Gabrieli, and Schmahmann, 2018a). Therefore, cerebro-cerebral connections that may give rise to indirect cerebro-cerebellar FC provide a means to expand the influence of the cerebellum (see Barton, 2012; Guell, Gabrieli, and Schmahmann, 2018a; Sokolov, Miall, and Ivry, 2017 for reviews). Pearson's full correlation can reflect those aspects better than partial correlation, which regresses out any indirect effect.

Dynamic Functional Connectivity

To model whole-brain FC dynamics, we applied the hidden Markov models (HMM) to the concatenated timeseries, across all subjects and runs, as implemented in the hidden Markov model multivariate auto-regression (HMM-MAR) toolbox https://github.com/OHBA-analysis/HMM-MAR. The HMM method is a generative

probabilistic modelling approach based on the principles of variational Bayesian inference that uncovers a set of hidden states that describe the observed timeseries and reoccur over time, taking into account the temporal ordering of the observed data points (Vidaurre, Smith, and Woolrich, 2017). The HMM bypasses the limitations of the commonly used sliding window and k-means clustering by directly inferring FC states at each timepoint in a self-contained manner (i.e., without "windowing") (Quinn et al., 2018; Vidaurre, Smith, and Woolrich, 2017). That is, the HMM determines temporal resolution or "window length" in a data-driven manner (Quinn et al., 2018). Moreover, unlike clustering techniques, the HMM accounts for the time-dependencies of the data and explicitly models the state transitions as a Markov chain, in that the next state is only dependent on the current state (i.e., model order=0) not past states (Quinn et al., 2018). Within the framework of the HMM, each state is modelled as a multivariate Gaussian distribution of observations at each timepoint with a mean representing a "spatial co-activation" pattern and a covariance matrix representing a FC pattern among brain regions (Vidaurre, Smith, and Woolrich, 2017). In this study, we were mostly interested in FC variations. Thus, we defined the states by their Pearson's full and partial correlation matrices rather than changes in regional activation. Additionally, the HMM estimated the transition probabilities between the states and the subject-specific state timecourses, which represented timeseries of pointwise probability for each state to be "active" at each timepoint for each subject (Quinn et al., 2018; Vidaurre et al., 2018).

Similarly to clustering methods, the HMM method does not represent a biophysical model and hence requires that the number of states be specified *a priori*. The commonly used criterion for choosing an "optimal" number of states is to compare different models in terms of goodness-of-fit using the free-energy index (Stevner et al., 2019). The free-energy is the cost function that the variational Bayesian inference aims to minimize, and is typically used for model comparison and selection (i.e., the lower the better). In this study, we assumed a fixed number of six states as a compromise, in terms of free energy, temporal resolution, and stability, between a lower-order model (5 states) and higher-order models (8, 10 and 12 states) after performing a stability analysis (Supplementary Section S3.3, Supplementary Figure S3.2). However, we were able to replicate our findings using the 5 and 8 states configurations (Supplementary Tables S3.2-S3.3). Finally, we generated surrogate (null) data to assess whether the observed state transitions are an exclusive property of the observed rsfMRI data or are due to mere resampling variations. The detailed description and results of this analysis are presented in Supplementary Material (Supplementary Figure S3.1).

Subject-Specific FC States and Temporal Variability

In order to estimate a descriptive summary measure of dynamic cerebro-cerebellar FC, we explored the manifestation of the group-level FC states at the subject level. In the group model, the states are common across subjects, whereas the state time-courses are subject-specific. So, in order to get a subject-specific description of the states, we performed a "dual-estimation" of the HMM (analogous to dual regression in the framework of GICA; Vidaurre et al., 2019). In particular, we re-applied the HMM to each subject's data using the initial group-level estimates and the subject-specific state timecourses as priors when updating and re-inferring the states. This procedure estimated a maximum of six FC states per subject, each represented by a full and a partial correlation matrix. Then, using these estimations, we recomputed the state timecourses and, ultimately, the frequency of occurrence of each state for each subject, defined as the total number of times each state was active during the scanning session (Vidaurre et al., 2019).

To compute the temporal variability of cerebro-cerebellar FC in each subject, we first calculated the statewise FC strength between cognitive cerebral RSNs and the cerebellum, similarly to the static FC analysis, using equation 3.1. Then, we calculated the temporal variability of FC, denoted V_i , between each cerebral RSN i and the cerebellum as the frequency-weighted standard deviation of the statewise strength scores from the static FC strength score, using the states' frequencies of occurrence as weights. This meant that more frequently "visited" states had more contribution to the final value of temporal variability, which was defined as follows:

$$V_{i} = \sqrt{\frac{\sum_{k=1}^{6} f_{k} \left(S_{ik} - \overline{S_{i}}\right)^{2}}{\sum_{k=1}^{6} f_{k} - 1}}$$
(3.2)

where $S_{i,k}$ is the strength of FC between cerebral RSN *i* and the cerebellum in state *k*, $\overline{S_i}$ is the time-averaged strength of FC between cerebral RSN *i* and the cerebellum, and the weight factor f_k is the frequency of occurrence of state *k*. As a result, the temporal variability index contained information about the absolute deviations in FC strength at short timescales combined with information about the time spent by each subject in each state.

2.7 Statistical Analysis

To test for associations between the different measures of cerebro-cerebellar FC and self-reported impulsivity, we used multivariate general linear models (GLMs) that included the different impulsivity variables as predictors and the FC measures (static and dynamic) as response variables in a multiple linear regression framework. All variables were orthogonalized with respect to age, gender, and meanFD to control for potential confounding effects imposed by these variables on the findings. To test for significance, we performed non-parametric permutation testing with 10,000 permutations and a maximum test-statistic procedure to obtain familywise error (FWE) adjusted p-values for all tests. In this context, subject labels in the observed data were randomly rearranged 10,000 times, GLMs were re-fitted in each rearrangement, and an empirical distribution of the maximum test-statistics (i.e., z-scores) obtained from all permutations was estimated. Then, a FWE-adjusted p-value was calculated for each test as the proportion of maximum z-scores that are greater than the observed z-score, z_0 , in the original, non-permuted data. This method has been shown to provide strong control of Type-I errors without being strictly conservative as is the case with conventional techniques that adjust for the family-wise error rate (e.g., Bonferroni) (Winkler et al., 2014). Finally, we reported significant associations with FWE-adjusted p < 0.05.

To further evaluate the generalizability and replicability of our inference framework, we used a repeated stratified 5-folds cross-validation scheme to split the initial sample into training (80% of data, 107 subjects) and testing (20% of data, 27 subjects) sub-samples where the proportion of males and females was preserved in each split. The cross-validation scheme was repeated 500 times with a different randomization in each repetition. Then, GLMs were fitted to the training data in each fold/repetition and then used to predict the outcomes (i.e., static and dynamic FC measures) in the testing data. Finally, we reported the median of the explained variance scores obtained in the training data, denoted R_{train}^2 , and testing data, denoted R_{test}^2 , across all folds and repetitions as indicators of the replicability of significant findings.

3 Results

3.1 Behavioral and Demographic Data

Summary statistics of demographic and behavioral data are provided in Table 3.1, whereas associations between the different self-reported measures of impulsivity are provided in Supplementary Table S3.1. Note that, although they theoretically assess distinct cognitive and behavioral constructs related to impulsivity, the different self-reported measures may exhibit strong relationships with each other, potentially biasing statistical inferences due to multicollinearity. Multicollinearity arises when there is a strong linear relationships between one or more of the independent variables in a multiple regression model (Farrar and Glauber, 1967). Thus, we tested for possible multicollinearity issues in the data by computing the variance inflation factor (VIF), which quantifies the severity of multicollinearity among the independent variables in a multiple regression model. A low VIF score close to 1 indicates the absence of collinear relationship between an independent variable and other variables present in the model. In this study, all self-reported impulsivity variables had a VIF < 2 except for the UPPS-P negative and positive urgency. Accordingly, in order to avoid potential multicollinearity effect due to the strong association between the two measures (Student's t = 11.34, r = 0.68, $p < 10^{-15}$),

Healthy Subjects (N=134, 62 females)								
	Mean	SD	Median	Min	Max	VIF	Correlation with age (r)	Gender difference (t)
Age	24	4	25	20	40	_		-0.464
meanFD	0.14	0.03	0.15	0.09	0.22	_	0.0028	0.1
PosUrg	1.9	0.5	1.9	1	3	2.5	0.07	0.13
NegUrg	2.2	0.5	2.2	1.2	3.3	2.3	-0.01	2.91*
Premed	2	0.4	2	1.1	3	1.3	-0.02	-0.74
Persev	2	0.5	1.9	1	3.2	1.36	0.04	-1.54
SenSeek	2.8	0.6	2.8	1.4	4	1.13	-0.18	-3.32**
BIS	20.5	3.1	21	12	28	1.15	-0.1	4.73**
BAS	37.2	3.7	37	28	47	1.22	0.1	0.45

TABLE 3.1: Demographics and Data Characteristics

 Note: SD: Standard deviation, VIF: Variance inflation factor, r : Pearson's correlation, t : Student's t, meanFD : mean framewise displacement, PosUrg: Positive urgency, NegUrg: Negative urgency, Premed: Lack of premeditation , Persev: Lack of perseverance, SenSeek: Sensation seeking, BIS: Behavioral inhibition system, BAS: Behavioral approach system.

* p < 0.05 , ** p < 0.01

we applied factor analysis to obtain one urgency factor that preserves a sufficient amount of variance in the data, while eliminating potential multicollinearity effects. The final set of self-reported measures of impulsivity included six variables: UPPS-P urgency, UPPS-P lack of premeditation, UPPS-P lack of perseverance, UPPS-P sensation seeking, behavioral inhibition system (BIS) and behavioral approach system (BAS). The normality of the variables was assessed using the Shapiro-Wilk test of normality, and departures from normality were counteracted using rank-based inverse Gaussian transform.

3.2 GICA Results

Cerebellum-only GICA

Resting-state fMRI data from the cerebellum were decomposed into 25 ICs, out of which 14 ICs were visually identified as cerebellar RSNs and illustrated in **Figure 3.1**. Eleven ICs were identified as noise and hence discarded from subsequent analysis. The RSNs were arranged into putative functional groups based on their anatomical or functional properties and overlap with previously established cerebellar functional clusters (Buckner et al., 2011). Specifically, the functional clusters were: sensorimotor, visual, attention, salience, fronto-parietal, default mode, and



Group-level Cerebellar RSNs

FIGURE 3.1: The identified cerebellar networks. Cer-latMot: Cerebellar lateral motor network, Cer-rMot: Cerebellar right motor Network, Cer-lMot: Cerebellar left motor network, Cer-mMot: Cerebellar medial motor network, Cer-Vis: Cerebellar visual network, Cer-DAN: Cerebellar dorsal attention network, Cer-SalVan: Cerebellar salience/ventral attention network, Cer-SN: Cerebellar salience network, Cer-DMN: Cereballar default mode network , Cer-LN: Cerebellar language network, Cer-IFPN: Cerebellar left fronto-parietal network, Cer-FPN: Cerebellar right fronto-parietal network

language. However, two cerebellar RSNs, whose spatial activation maps were well situated in the GM, did not overlap with well-known cerebellar functional clusters. These were labelled as "Vermis" and "Crus-I/II" based on the anatomical landmarks that overlap with their spatial activation maps. Moreover, taking into consideration the contralateral representation of large-scale networks in the cerebellum, labels of unilateral cerebellar RSNs were inverted. For instance, if spatial activation was mostly localized in the left anterior cerebellum, the naming would be cerebellar right motor network (Cer-rMot) due to the inverted sensorimotor map present in the anterior cerebellar lobe.

Cerebral GICA

Resting-state fMRI data from the cerebral cortex and sub-cortex were decomposed into 30 ICs out of which 25 ICs were identified as non-artifactual RSNs based on visual inspection of the localization of spatial activation in the grey matter (GM) and illustrated in **Figure 3.2**.



FIGURE 3.2: The identified large-scale cerebral networks. BGN: Basal ganglia network, Thal: Thalamus, latMot: Lateral motor network, rMot: Right motor Network, lMot: Left motor network, mMot: Medial motor network, exVis: Extra-striate visual network, mVis: Medial Visual network, oVis: Occipital Visual Network, lVis: Lateral visual network, Aud: Auditory network, pCun/PCC: Precuneus/Posterior cingulate cortex network , DAN: Dorsal Attention Network, TPN: Task positive network, SalVAN: Salience-ventral attention network, AccSN: Anterior cingulate cortex salience network, FSN: Frontal salience network, cFPN: Central fronto-parietal network, rFPN: Right fronto-parietal network, lFPN: Left fronto-parietal network, dDMN: Dorsal default mode network, vDMN: Ventral default mode network, LN: Language network, vmOFN: Ventro-medial orbito-frontal network

3.3 Strength of Cerebro-Cerebellar FC Predicts BIS/BAS

We found significant associations (i.e., FWE-adjusted p-values < 0.05) between the strength of cerebro-cerebellar (partial correlation) FC and self-reported measures of impulsivity. Particularly, results revealed a negative correlation between behavioral inhibition system (BIS) and the strength of FC between the cerebellum and the basal ganglia network (BGN, z = -3, $\beta = -0.31$, p = 0.038, $R_{train}^2 = 0.07$, $R_{test}^2 = 0.068$) and a negative correlation between the behavioral approach system scale (BAS) and the strength of FC between the cerebellum and the frontal salience network (FSN, z = -3.1, $\beta = -0.29$, p = 0.033, $R_{train}^2 = 0.08$, $R_{test}^2 = 0.073$). These findings are presented in **Table 3.2** and the corresponding scatter plots are illustrated in **Figure**





FIGURE 3.3: Scatter plots of significant associations between the strength of cerebrocerebellar FC and self-reported impulsivity, assessed using the BIS/BAS scales. (A) Values of FC strength between the frontal salience network (FSN) and the cerebellum plotted against the individual self-report scores on the Behavioral Approach System (BAS). (B) Values of functional connectivity strength between the basal ganglia and the cerebellum plotted against the individual self-report scores on the Behavioral Inhibition System (BIS). Variables were adjusted for age, gender, and meanFD and presented as z-scores. β : standardized regression coefficient, *p*: FWE-adjusted p-value

Temporal Variability of Cerebro-Cerebellar FC Predicts UPPS-P Sub-Scales

We found significant associations between the temporal variability of cerebrocerebellar (full correlation) FC and self-reported measures of impulsivity. Particularly, results revealed negative correlations between UPPS-P lack of premeditation and the temporal variability of FC between the cerebellum and both the FSN (z = -3.5, $\beta = -0.34$, p = 0.008, $R_{train}^2 = 0.092$, $R_{test}^2 = 0.09$) and the precuneus/posterior cingulate cortex network (pCun/PCC, z = -3.7, $\beta = -0.36$, p = 0.003, $R_{train}^2 = 0.11$, $R_{test}^2 = 0.096$). Moreover, results revealed positive correlations between UPPS-P sensation seeking and the temporal variability of FC between the cerebellum and the FSN (z = 3.3, $\beta = 0.32$, p = 0.019, $R_{train}^2 = 0.078$, $R_{test}^2 = 0.08$), pCun/PCC (z = 3.6, $\beta = 0.35$, p = 0.005, $R_{train}^2 = 0.093$, $R_{test}^2 = 0.086$), BGN (z = 3.1, $\beta = 0.3$, p = 0.037, $R_{train}^2 = 0.078$, $R_{test}^2 = 0.063$), and thalamus (z = 3.3, $\beta = 0.32$, p = 0.019, $R_{train}^2 = 0.078$, $R_{test}^2 = 0.074$). Significant findings are



presented in Table 3.2 and the corresponding scatter plots are illustrated in Figure 3.4.

FIGURE 3.4: Scatter plot representations of significant associations between the temporal variability of cerebro-cerebellar FC and self-reported impulsivity. Values of temporal variability of FC between cerebellum and the (A) frontal salience network (FSN) and (B) precuneus/posterior cingulate cortex network (pCun/PCC) plotted against the individual self-report scores on the UPPS-P lack of premeditation sub-scale. Values of temporal variability of FC between the cerebellum and (C) FSN, (D) pCun/PCC, (E) BGN, and (F) thalamus plotted against the individual self-report scores on the UPPS-P sensation seeking sub-scale. All variables were adjusted for age, gender, and meanFD and presented as standardised z-scores. β : standardized regression coefficient, *p*: FWE-adjusted p-value

4 Discussion

Growing evidence associates cerebellar damage and pathological cerebro-cerebellar dysfunction with abnormal levels of impulsivity caused by deficits in executive function and an imbalance between top-down control and bottom-up reward processes. However, little is known about the relation between cerebro-cerebellar functioning and impulsivity in healthy adults, which can potentially inform future investigations into the neurobiology of cognitive deficits associated with impulsivity.

Network	FC Aspect	Impulsivity Scale	Z	β	р	R^2_{train}	R_{test}^2
BGN-Cerebellum	Strength	BIS	-3	-0.31	0.038	0.07	0.068
	Variability	SenSeek	3.1	0.3	0.037	0.068	0.063
Thal-Cerebellum	Variability	SenSeek	3.3	0.32	0.019	0.078	0.074
FSN-Cerebellum	Strength	BAS	-3.1	-0.29	0.033	0.08	0.073
	Variability	Premed	-3.5	-0.34	0.008	0.092	0.09
	Variability	SenSeek	3.3	0.32	0.019	0.078	0.08
pCun/PCC-Cerebellum	Variability	Premed	-3.7	-0.36	0.003	0.11	0.096
	Variability	SenSeek	3.6	0.35	0.005	0.093	0.086

TABLE 3.2: Significant Associations Between Cerebro-Cerebellar FC and Self-Reported Impulsivity

Note: **Strength**: Time-Averaged Strength of FC, **Variability**: Temporal variability of FC, *z*: *z*-statistic, β : standardized regression coefficient, *p*: family-wise error adjusted p-value, R_{train}^2 : median of explained variance in the training data, R_{test}^2 : median of explained variance in the testing data

Accordingly, we set out to examine whether different aspects of cerebro-cerebellar FC at different timescales could relate to different forms of self-reported impulsivity in healthy young adults. Using static and dynamic FC analysis approaches, we found evidence that behavioral inhibition, behavioral approach, lack of premeditation and sensation seeking are associated with the strength and temporal variability of FC between the cerebellum and multiple brain networks encompassing prefrontal, parietal, and subcortical regions involved in executive control, salience attribution, and reward processing. Non-parametric permutation testing and crossvalidation supported the statistical significance and cross-validity of the current findings, respectively. Together, our findings suggest that the cerebellum could play an integral role in the circuits subserving the integration of a heterogeneous mixture of cognitive and affective functions related to impulsivity. Importantly, the study highlights the utility of complementing time-averaged (i.e., static) measures of FC with time-resolved (i.e., dynamic) FC analysis in furthering current understanding of the neurobiological underpinnings of complex traits and the functional repertoire of the cerebellum and the cerebro-cerebellar system. We further discuss the findings, limitations and future directions of the study in the following subsections.

4.1 Static Cerebro-Cerebellar FC and Impulsivity

Results of the static FC analysis revealed a significant negative correlation between the behavioral inhibition system (BIS) and the strength of the direct FC between the cerebellum and the basal ganglia network (BGN). According to Gray's theory (Gray, 1991), a high activity of the BIS is expressed as an increase in sensitivity towards negative cues and outcomes, resulting in avoidance behavior. Thus, our finding suggests that stronger BGN-cerebellar FC in healthy individuals is associated with less avoidance of actions with potentially negative or aversive outcomes and comports with previous findings implicating both the cerebellum and the basal ganglia in the circuits that underlie inhibitory executive control of evaluated actions (Brunamonti et al., 2014). Traditionally, the basal ganglia and the cerebellum have been assigned to complementary roles within the sensorimotor domain. However, recent findings show that both structures are reciprocally interconnected with each other and with multiple cortical regions (Bostan and Strick, 2010), which allows for a joint modulatory influence on cognitive and limbic functions, notably in reward/punishment learning mechanisms (see Pierce and Péron (2020) for a recent review). In this context, previous studies have shown that increased striatocerebellar connectivity is associated with increased impulsivity in patients with attention deficit hyperactivity disorder and substance use disorders (Miquel et al., 2019; Oldehinkel et al., 2016; Ruitenberg et al., 2018), suggesting this to index an imbalance between top-down and bottom-up influences on behavior. The consequence of this imbalance is an over-reliance on motivated "Go" brain mechanisms at the expense of "No-Go" behavioral inhibition mechanisms, indicating an underactive BIS (see Miquel et al. (2019) for a review).

Furthermore, results revealed a significant negative correlation between the behavioral approach system (BAS) and the strength of the direct FC between the cerebellum and the frontal salience network (FSN). Unlike the BIS, the behavioral activation system (BAS) is based on a model of appetitive motivation, reflecting an individual's disposition to pursue reward and engage in goal-directed behaviors (Gray, 1991). This suggests that stronger FC between the cerebellum and the FSN in healthy individuals is associated with less activation of approach behaviors towards rewards and hence increased top-down control over goal-directed behaviors. The identified FSN encompasses regions of the dorsolateral prefrontal cortex, frontopolar cortex, dorsal anterior cingulate cortex, anterior insula, and posterior parietal cortex (see Figure 3.6). These regions are known to be involved in directing attention towards important stimuli, selecting appropriate responses to salient stimuli, and integrating relevant sensory, emotional, and cognitive information (Corbetta and Shulman, 2002; Uddin, 2016). The cerebellum might play an important role in the prediction of the outcome of responses to stimuli and coordinate the streams of information integrated by the FSN, thereby promoting prefrontal functionality in top-down cognitive control (Miquel et al., 2019). In this context, previous studies have shown that frontocerebellar dysconnectivity in certain brain disorders marked an active BAS, notably substance addiction, is associated with deficits in impulse control, cognitive planning and attentional set shifting (Jung et al., 2014; Miquel et al., 2019; Sullivan and Pfefferbaum, 2005). Thus, the strength of FC between the cerebellum and FSN may be informative of potential predisposing factors for vulnerability to certain psychopathology characterized by an over-activation of the BAS.

It is worth noting that although we calculated a summary measure of cerebrocerebellar FC strength averaged over the whole cerebellum, the FSN was found to predominantly connect with the cerebellar salience network (Cer-SN) that overlapped with posterolateral regions of the cerebellum, whereas the BGN predominantly connect with the Vermis network that overlapped with the posterior cerebellar vermis, at the group level (see Figure 3.5). Previous fMRI studies have shown that the posterolateral cerebellum is mostly devoted to association networks such as the salience and executive control network (Buckner et al., 2011; Habas et al., 2009), whereas the posterior vermis is mainly involved with the limbic system and directly connects to the ventral tegmental area, which is the center of dopaminergic cell bodies (Carta et al., 2019). Moreover, lesions to the posterolateral cerebellum and the posterior vermis have been shown to induce an an array of behavioral disturbances including, among others, impulsiveness and behavioral disinhibition (Schmahmann, Weilburg, and Sherman, 2007; Kim et al., 2013; Miquel et al., 2019).



FIGURE 3.5: (A) The group-average partial correlation FC matrix and the cerebro-cerebellar sub-matrix. (B) A circular graph of the extracted sub-matrix showing the strongest direct cerebro-cerebellar links at the group level

These results, along with the present findings, suggest that these cerebellar networks (i.e., Cer-SN and Vermis) take part in the circuits influencing the motivational systems that regulate responses to cues signaling reward and aversion. However, since we discuss results related to undirected FC, a causal effect of the cerebellum can only be speculated and will require future studies involving measures of causal influences such as effective connectivity (Friston, 2011).

4.2 Dynamic Cerebro-Cerebellar FC and Impulsivity

Results of the dynamic FC analysis revealed that the UPPS-P lack of premeditation sub-scale—which measures the tendency to act rashly without reflection upon the potential consequences of an action—was negatively correlated with the temporal variability of FC between the cerebellum and two brain networks, the FSN and the precuneus/posterior cingulate cortex network (pCun/PCC). The identified pCun/PCC network includes sub-regions of the dorsal and central precuneus and the dorsal posterior cingulate cortex (Figure 3.6), which are classified as parts of the executive control network (Yeo et al., 2011). Although the traditional functional



FIGURE 3.6: Group-level (A) FSN and (B) pCun/PCC networks

characterization of the precuneus and the PCC arises from their roles within the DMN, studies have revealed that the dorsal PCC is a highly dynamic region showing selective FC across a range of networks, most notably frontoparietal networks involved in top-down cognitive control (Leech, Braga, and Sharp, 2012; Leech and Sharp, 2013). In particular, the dorsal PCC tunes the "metastability" of the brain as a whole, by dynamically linking networks, that are functionally distinct but exhibit coordinated changes in activity, to allow for cost-efficient allocation of resources across the brain (Lee, Smyser, and Shimony, 2013). Thus, our finding suggests that greater switching of resting-state FC, driven by state transitions, between the cerebellum and integrative "multi-network" regions predicts an increased tendency to make thoughtful decisions not dominated by spontaneity. This might mean that thoughtful decision making requires higher levels of dynamic functional interactions, during rest, between the cerebellum and multiple demand networks to ameliorate adaptive reconfigurations of brain states in support a greater control over immature impulses once an action is anticipated.

Furthermore, we found significant positive correlations between the UPPS-P sensation seeking—which measures the tendency to seek new and rewarding experiences—and the temporal variability of FC between the cerebellum and four brain networks, the FSN, pCun/PCC, BGN, and the thalamus network. This finding suggests that greater switching of resting-state FC between the cerebellum and integrative brain regions predicts an enhanced salience attribution to novel and exciting experiences. The regions belonging to this ensemble of networks are wellknown connector hubs (Hwang et al., 2017; Heuvel and Sporns, 2013), central for the integration of resources from across the brain and play pivotal roles in a wide range of cognitive functions including those underlying sensation seeking, such as top-down cognitive control and bottom-up reward/saliency evaluation (Cheng et al., 2015). The balance in the interplay of these processes may explain individual differences in sensation seeking (Cheng et al., 2015). Thus, in an analogous argument to the previous finding, the cognitive processes underlying sensation seeking might require dynamic functional interactions of top-down control and bottom-up reward/saliency networks with the cerebellum, to adaptively reconfigure attention and actions once a potentially salient stimuli is anticipated.

Broadly, these findings suggest that measures of dynamic FC between the cerebellum and integrative brain networks, that act as "funnels" of information streams across the brain, can reveal information about the functional repertoire of the cerebro-cerebellar system not captured by time-averaged measures. More-over, these findings comport with the hypothesis that the cerebellum and cerebro-cerebellar networks take part in large-scale integrative brain systems that operate in conjunction to support embodied cognition Barton (2012). In this configuration, cerebellar resources might be recruited at fast timescales to maintain a well-calibrated flow of information and a homeostatic balance between top-down cognitive control and bottom-up reward processes, which preserves impulsivity-related

traits in a "healthy" range. Importantly, since we only included healthy individuals with no past nor present psychiatric conditions, it was not possible to discern whether temporal variability of FC within the implicated networks relates to pathological sensation seeking, for instance. However, these findings might provide a starting point for future studies focusing on cerebro-cerebellar dynamic interactions in brain disorders marked by impulsive symptomatology, such as alcohol use disorder or ADHD (Jung et al., 2014; Miller et al., 2010). Moreover, since we analyzed the dynamics of undirected FC, the interpretations of the current findings are limited. Hence, causal links or modulatory effects within the implicated cerebro-cerebellar networks cannot be concluded in this case, and future investigations are needed to make such inferences. Nonetheless, these results constitute empirical evidence suggesting that complex processes underlying different impulsivity traits are mediated by extended cognitive control and reward/saliency systems encompassing cerebellar functional modules, potentially as adaptive modulators of information flow and cognitive state transitions.

4.3 Limitations and Future Perspectives

Developing an understanding of the dynamics of cerebro-cerebellar connectivity in healthy individuals may have future implications for explaining adaptive cognitive control mechanisms, reward/aversion processing, and a variety of brain disorders featuring impulsive symptomatology and cerebro-cerebellar dysconnection. In this sense, the main focus of this study was to test whether inter-individual differences in normal trait impulsivity relate to static and dynamic cerebro-cerebellar FC in healthy individuals. Although we found evidence that supported the hypothesis, the correlational nature of our analysis precludes the inference of any causal or directed relationship. A comprehensive understanding of the cerebellar role in impulsivity will require future research involving causal analysis of cerebro-cerebellar time-resolved extensions (Park et al., 2018) of effective connectivity, dynamic causal modelling, psychophysiological interaction analysis, or causative manipulation of

cerebellar activity to make more insightful inferences of a direct cerebellar involvement in regulating impulsivity. In the same sense, another limitation is the lack of objective measurements of impulsivity such as behavioral tasks (e.g., Go/No-Go task, Stop-Signal task, reward devaluation tests), which could have provided a more controlled and, potentially, less biased perspective of individual differences in impulsivity. Future investigations using dynamic FC methods should explore gender and age differences and include individuals diagnosed with neuropsychiatric disorders that are known to feature a co-occurrence of cerebro-cerebellar dysfunctioning and impulsive symptomatology.

Other limitations regarding choices of methodology are also noteworthy. One limitation is the use of low-dimensional spatial decompositions of both the cerebrum and cerebellum that only identified large-scale RSNs in both structures. The choice of low-dimensional representations was driven by the fact that the number of parameters to be estimated by the HMM increases exponentially when the number of channels (i.e., brain regions) becomes higher, which in turn inflates computational complexity and, given a moderate sample size, significantly minimizes the stability of the HMM across different runs (Quinn et al., 2018). However, finegrained representations of the brain can decompose large-scale RSNs further into smaller sub-networks that enable a more accurate mapping between dynamic FC and impulsivity. For instance, high-dimensional representations may reveal further sub-cortical regions that are not independently observed in low-dimensional parcellations, such as the amygdala, hippocampus, and nuclei of the brain stem, which are key components of the limbic system subserving in emotion regulation and, hence, regulating impulsive behavior. Developing new methods or augmenting existing ones to reliably process high-dimensional data is needed in order to overcome this limitation.

Along a similar line, a potential limitation is that we restricted our analysis to the overall cerebellar "influence" within distinct large-scale brain systems, which, although appropriate with respect to our hypothesis, precluded a direct and detailed mapping between different forms of impulsivity and specific cerebellar-based networks. However, this choice was driven by on several reasons. First, cerebellar regions exhibit strikingly similar anatomical properties and are believed to

perform universal computations across the sensorimotor, cognitive, and affective domains, regardless of the fact that they communicate with different brain regions (chmahmann2019cerebellum; Guell, Gabrieli, and Schmahmann, 2018a). Second, in a recent study, Marek et al. (2018) have revealed that the cerebellum seems to follow a common organizational principle at the group level, but cortical functional network representations within the cerebellum are highly individual-specific in terms of shape, size and location. Additionally, individual variations in shape and exact location of brain regions strongly influences the modelling of brain connectivity (Bijsterbosch, Smith, and Beckmann, 2017). For these reasons, we did not impose a group effect on the computation of summary measures by assuming a single one-to-one mapping between cerebral and cerebellar RSNs based on a "winner-takes-all" strategy that discards potentially meaningful weaker connections that arise due to individual variability. Nonetheless, exploring the unique contributions of different cerebellar modules to disparate cognitive domains and personality traits may be of interest for future studies in the light of recent hypotheses of "multiple cerebellar functionality" (Diedrichsen et al., 2019). This will require using individualized cerebellar parcellations, computed using precision functional mapping techniques (Gordon et al., 2017), to accurately map cerebellar networks at the individual level and better understand their unique contributions.

5 Conclusion

In this study, we have shown that multiple subfacets of trait impulsivity are associated with both static and dynamic aspects of cerebro-cerebellar FC, during restingstate. Importantly, this study sheds new light on the cognitive and behavioral relevance of dynamic reconfigurations, driven by changes in FC states during rest, between the cerebellum and large-scale brain networks. Together, the findings might have future implications for predicting predisposing factors to certain psychopathology characterized by impulsive symptomatology. Our results also point out the importance of complementing time-averaged measures with time-resolved analysis of FC for comprehensively understanding the functional repertoire of the cerebellum and the cerebro-cerebellar system.

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Author Contributions

Majd Abdallah : Study Design, Writing, Functional Connectivity Analysis, Statistical Analysis, and Visualization. **Nicolas Farrugia**: Study Design, Statistical Analysis, Revision of the Manuscript, and Supervision. **Valentine Chirokoff**: Statistical Analysis. **Sandra Chanraud**: Study Design, Revision of the Manuscript, Obtaining Funding, and Supervision.

Supplementary Material For Chapter 3

S3.1 Self-Reports of Impulsivity

The partial correlation coefficients between the different self-reports of impulsivity are summarized in Table S3.1, below.

	PosUrg	NegUrg	PreMed	Persev	SenSeek	BIS	BAS
PosUrg		0.63***	0.16	0.16	0.00	-0.03	0.10
NegUrg			0.05	0.08	-0.03	0.3**	-0.02
PreMed				0.28***	0.23**	-0.23**	0.00
Persev					0.04	0.16	-0.37***
SenSeek						-0.13	0.25**
BIS							-0.00

 TABLE S3.1: Partial Correlation Coefficients Among Impulsivity

 Scales Assessed by Multiple Linear Regression

Notes *PosUrg*: Positive Urgency, *NegUrg*: Negative Urgency, *Premed*: Lack of Premeditation, *Persev*: Lack of Perseverance, *SenSeek*: Sensation Seeking, *BIS*:Behavioral Inhibition System, *BAS*:

Behavioral Approach System.

*p < .05 , **p < .01 ,***p < .001

S3.2 Assessment of Genuine FC State Transitions

We examined whether the state transitions are a genuine and exclusive property of the observed rsfMRI data and are not attributable to resampling variations by generating surrogate "null" data. Like any generative model, the HMM can be used to generate surrogate data that follow the same distribution as the observed data and preserve the first-order statistics, the autocorrelation structure, the time-averaged FC, power spectral density, and amplitude distribution, but presumably lack the property of biological interest, which is, in this case, state transitions (Vidaurre, Smith, and Woolrich, 2017; Zalesky et al., 2014). In this sense, we fitted a multivariate Gaussian distribution, that matched the observation model used by the HMM, to each subject's rsfMRI timeseries to generate 100 surrogate null datasets that comprised the same amount of data (i.e., 1 hour, four runs, and TR=1400 ms). Then, we applied the HMM, with unchanged parameters, to the null data and estimated a metric that enabled a straightforward comparison of the estimated dynamics with those estimated in the observed rsfMRI data.

One informative metric that has been used in a previous study (Vidaurre, Smith, and Woolrich, 2017) is the maximum fractional occupancy. Fractional occupancy (FO) is defined as the proportion of time a state is visited across the scanning session, whereas maximum fractional occupancy (maxFO) is simply the proportion of time the predominantly occurring state is visited (Vidaurre, Smith, and Woolrich, 2017). Thus, high values of maxFO (close to 1) indicate that almost a single state describes the data and hence the absence of any time-dependent structure or state transitions. In contrast, low values of maxFO (closer to 0 than 1) indicate that multiple recurring states describe the data and hence the presence of structured timedependencies in FC. In this sense, when applied to the surrogate data, the HMM should not reveal any meaningful state transitions, and maxFO scores should be close to 1. However, if the HMM captured state transitions in the null data like those in the observed data, then the whether the In this context, we compared the distributions of maxFO scores aggregated from all subjects and runs in the real data to those obtained in the 100 null datasets to assess the presence of state transitions that are an exclusive property of the real rsfMRI data.

The distribution of maxFO and the group-averaged frequency of occurrence of each state suggest the presence of genuine FC state transitions in the real data as opposed to the simulated (null) data that were mostly described by a single dominant state (Figure S3.1). These findings indicate that the time-varying structure of FC is a genuine characteristic of the real rsfMRI, despite the fact that the real and simulated data share identical time-averaged FC profiles.



FIGURE S3.1: Dynamic FC analysis results. A) Group-level FC states. At the top of each matrix is the group-averaged fractional occupancy (FO), which represents the percentage of time each state is visited over all subjects. B) Maximum fractional occupancy distributions in the real rsfMRI dataset (left) and the surrogate null datasets (right). A straightforward comparison of the profiles of both distributions suggests that state transitions are a property of the real rsfMRI data and do arise due to resampling variability.

S3.3 Hidden Markov Models: Stability Analysis

Previous studies that have used hidden Markov modelling of whole-brain FC dynamics estimated between 5 and 12 brain states using different criteria and datadriven techniques (Baker et al., 2014; Ou et al., 2015; Vidaurre, Smith, and Woolrich, 2017; Vidaurre et al., 2018; Kottaram et al., 2019; Karapanagiotidis et al., 2018). In this study, we considered testing the stability of models with 5, 6, 8, 10, and 12 states by running the HMM 100 times in each case and estimating the degree of similarity between the different runs, measured as the pairwise correlation between the state timecourses when the states are optimally aligned (across runs) via the Hungarian algorithm (Munkres, 1957). We performed 100 runs of each configuration because of the heuristic nature of the Bayesian inference process, which is very sensitive to slightly varying initial conditions and might converge to different local minima in each run, leading to different conclusions in each run (Quinn et al., 2018). Thus, the stability or consistency of a certain model is crucial in order to obtain reliable and interpretable findings. In this sense, if the state timecourses across different runs were highly similar, then a model seems to be consistently converging towards a global minima in each run.

As expected, lower-order models (5 and 6 states) were more stable across runs than higher-order models (8, 10, and 12 states). This is because the parameter space enlarges exponentially as the number of assumed states increases, which decreases the likelihood of the algorithm to converge to a global minima across different runs (Quinn et al., 2018). However, we found that high-order models attained relatively lower free energy indices of goodness-of-fit than low-order models. Accordingly, we decided, as a compromise between stability, goodness-of-fit, and temporal resolution, to use the 6 states model, which was significantly more stable than higherorder models and attained a lower free energy index than the 5 states model.

Finally, out of the 100 HMM runs with 6 states, we chose the optimal solution that corresponded to the lowest free energy index as the final estimate of grouplevel FC states. Figure S3.2 illustrates the similarity (or stability) matrices that encode pairwise correlation coefficient between the state timecourses of 100 runs of the HMM with a different number of assumed states.





Similarity between Static and Dynamic FC Matrices

Computing the temporal variability of resting-state cerebro-cerebellar FC using the subject-specific FC states was based on our observation that static FC matrices highly resembled the frequency-weighted mean of the dynamic FC matrices: cosine similarity > 0.98 on average over all subjects. A bar chart showing the cosine similarity between the static FC matrix (full correlation) and the frequency-weighted mean of the dynamic FC matrices (full correlation) for each subject is illustrated in Supplementary Figure S3.3 below.



FIGURE S3.3: Cosine similarity between the static FC matrix and the frequency-weighted mean of the dynamic FC matrices for all subjects (Mean= 0.986)

S3.4 Results Obtained Using the 5 and 8 States HMM Configurations

To assess the robustness of our findings to varying analysis setting, we repeated the same analysis using 5 and 8 states HMM configurations. First, we selected, out of 100 runs of HMM in each case, the run the corresponded to the lowest value of free energy and then we estimated the subject-level FC states and the temporal variability of cerebro-cerebellar FC. The results reflected qualitatively similar patterns of associations between the dynamics of cerebro-cerebellar FC (full correlation) and the self-reported measures of impulsivity as those observed in the 6 states configuration. The statistical details of significant associations are reported in the Tables S3.2 and S3.3 below. Note that we did not correct for multiple comparisons in this validation step.

Network	Impulsivity Scale	Z	β	p-value
FSN-Cerebellum	Premed	-3.4	-0.33	0.001
	SenSeek	3.1	0.31	0.002
pCun/PCC-Cerebellum	Premed	-3.6	-0.34	<.001
	SenSeek	3.6	0.36	<.001
BGN-Cerebellum	SenSeek	3	0.29	0.003
Thal-Cerebellum	SenSeek	2.8	0.28	0.005

TABLE S3.2: Results obtained using the 5 states HMM configuration

TABLE S3.3: Results obtained using the 8 states HMM configuration

Network	Impulsivity Scale	Z	β	p-value
FSN-Cerebellum	Premed	-2.1	-0.22	0.045
	SenSeek	2.5	0.26	0.027
pCun/PCC-Cerebellum	Premed	-2.9	-0.28	0.007
	SenSeek	3.6	0.36	<.001
BGN-Cerebellum	SenSeek	2.6	0.27	0.008
Thal-Cerebellum	SenSeek	3.1	0.31	0.002

Chapter 4

Altered Cerebro-Cerebellar Resting-State Functional Connectivity

Dynamics in Alcohol Use Disorder

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Abstract

Alcohol use disorder (AUD) is widely associated with alterations in the cerebellum and cerebrocerebellar networks, contributing to an array of cognitive deficits. Resting-state functional connectivity (FC) analysis has been widely used to characterize these alterations, but almost all findings have been based on time-averaged measures of FC that do not address the dynamic nature of the human brain. In recent years, the "static" approach has been challenged with a growing interest in approaches that assess fast, dynamic changes in FC at fast timescales. In this domain, findings suggest links between "dynamic" FC and attention, learning, memory, cognitive flexibility, executive function and brain disorders, such as substance use disorders. Yet, little is known about the dynamics of cerebro-cerebellar resting-state FC, especially in AUD. Here, we analyzed resting-state functional magnetic resonance imaging data collected from AUD patients (N=18) and age- and sexmatched controls (N=18) using sliding window analysis and multilayer community detection. We assessed group differences in the dynamics of cerebro-cerebellar resting-state FC. Particularly, we compared groups in terms of temporal variability of cerebro-cerebellar FC and two measures of time-varying community structure: flexibility and integration, computed in the cerebellum as well as large-scale brain networks, in an exploratory analysis. Additionally, we evaluated the association between aberrant cerebro-cerebellar FC dynamics and an index of AUD symptom severity. Results revealed that, relative to controls, the AUD group exhibited significantly greater temporal variability of FC between the cerebellum and both the frontoparietal and ventral attention networks, indicating an abnormal hypervariability in resting-state FC within cerebro-cerebellar executive control and attention circuits in AUD. Moreover, we found that the AUD group exhibited significantly less flexibility and greater integration of cerebellar nodes than controls, which might reflect compensatory remapping or maladaptive plasticity in the cerebellum. Finally, exploratory analysis revealed significant group differences in flexibility and integration at the level of large-scale cognitive networks including the fronto-parietal, salience, and cingulo-opercular networks, suggesting abnormalities and disorganization in the time-varying community structure. Together, our findings bring evidence of selective and widespread alterations in cerebro-cerebellar FC dynamics during rest, which might have future implications for explaining features of the development of cognitive deficits in AUD and improving our understanding of the functional network organization of the brain with addiction.

4.1 Introduction

Alcohol use disorder (AUD) is a chronic and relapsing condition, characterized by uncontrolled consumption of dangerous amounts of alcohol, inducing a spectrum of effects on the central nervous system (Sullivan, Harris, and Pfefferbaum, 2010). Three decades of magnetic resonance imaging (MRI) studies have extensively have highlighted the negative consequences of AUD on selective brain regions and large-scale networks, providing a non-invasive, in vivo view of the neurobiological underpinnings of executive dysfunction, impulsive decision making, compulsive alcohol seeking, and the emotional distress associated with alcoholism (Chanraud and Bernard, 2015; Gilman et al., 2008; Jung et al., 2014). In this context, evidence suggests that the cerebellum and its circuits, notably the frontocerebellar circuitry, are highly vulnerable to alcohol-induced damage (Rogers et al., 2012; Sullivan and Pfefferbaum, 2005; Zahr, Pfefferbaum, and Sullivan, 2017). In short, structural MRI studies have reported significant reduction in gray matter volumes in the cerebellum (Sullivan and Pfefferbaum, 2005), and have found substantial damage to cerebro-cerebellar white matter pathways associated with the severity of alcohol dependence (De Bellis et al., 2005; Pfefferbaum et al., 2014; Yeh et al., 2009). Moreover, studies that use functional MRI to measure blood-oxygenlevel-dependent (BOLD) brain activity, during task performance and resting-state (rsfMRI), have reported abnormal activity in the cerebellum as well as disrupted patterns of cerebro-cerebellar functional connectivity (FC), associated with impairments of selective cognitive processes in AUD (Chanraud et al., 2011; Chanraud et al., 2013; Desmond et al., 2003; Rogers et al., 2012; Tapert et al., 2001; Wilcox et al., 2014).

The cerebellum is traditionally known for its role in motor control and learning (Manto et al., 2012). Over the past three decades, however, extensive evidence, notably from fMRI studies, has revealed that the majority of the cerebellum communicates with large-scale cognitive networks, suggesting a critical role for the cerebellum in cognitive and emotional functions (Barton, 2012; Buckner et al., 2011; Buckner, 2013; Guell, Gabrieli, and Schmahmann, 2018b; Guell et al., 2018). In this context, the cerebellum is believed to control cognitive processes, in a similar way

to controlling movements, thereby maintaining efficient cognitive processing and, ultimately, behavior around a homeostatic baseline (Buckner, 2013; Schmahmann, 2019; Sokolov, Miall, and Ivry, 2017). In AUD, however, selective cognitive and affective processes are impaired and deemed as inefficient, possibly due to the disorganization of information flow in the brain caused, at least in part, by altered FC within cognitive cerebro-cerebellar closed-loop circuits in general and frontocerebellar circuits in particular (Bernardin, Maheut-Bosser, and Paille, 2014; Chanraud et al., 2011; Oscar-Berman and Marinković, 2007). Studies have also shown that AUD patients performing well on tasks tend to recruit unaffected cerebro-cerebellar loops to compensate for functional degradation of brain networks normally used by controls for task performance, suggesting compensatory functional reorganization within the brains of AUD patients (Chanraud et al., 2013). These findings are predicated on observations of reduced FC within certain frontocerebellar executive control loops that is paralleled by an increase in FC strength within adjacent unaffected loops (Chanraud et al., 2011; Chanraud et al., 2013). Thus, AUD patients may need to integrate more brain regions, especially within the cerebellum, to complete a given cognitive task, which might compromise their ability to multitask (Sullivan, Harris, and Pfefferbaum, 2010).

Yet, most of our understanding of the role of cerebro-cerebellar networks in AUD comes from studies treating FC as a "static" quantity that does not change across a scanning session lasting five minutes or more. This approach, however, is blind to the fact that the brain is a dynamic structure, continuously integrating information and rapidly reconfiguring its intrinsic organization to refine internal representations of the environment and execute adaptive behaviors (Breakspear, 2017). In other words, the analysis of time-invariant FC is believed to average out meaningful variations in FC at timescales much shorter than a typical fMRI scan (Calhoun et al., 2014; Zalesky et al., 2014). In response to this shortcoming, studies have begun exploring "dynamic" FC, with findings indicating that the brain navigates through a set of transiently recurring FC configurations that encode fast changes in cognitive state, even during rest (Allen et al., 2014; Calhoun et al., 2014; Rashid et al., 2014; Vidaurre et al., 2018). Furthermore, dynamic FC has been shown to predict individual differences in complex cognitive processes, such as skill learning

(Bassett et al., 2011), executive functioning (Braun et al., 2015), attention (Fong et al., 2019), and cognitive flexibility (Douw et al., 2016) better than static FC, and to exhibit alterations in a number of brain disorders including, among others, autism (Harlalka et al., 2019), schizophrenia (Braun et al., 2016; Sakoğlu et al., 2010) and substance use disorders (Vergara et al., 2018).

Few studies have investigated the impact of excessive alcohol use on brain dynamics, with findings showing significant alterations in sensorimotor control regions (Vergara et al., 2018), the orbitofrontal cortex and insula (Hong et al., 2018), and, recently, frontostriatal circuits (Gerchen et al., 2020), associated with the level of alcohol consumption and poor cognitive performance in alcoholics. Furthermore, recent findings (Abdallah et al., 2020), in a large sample of healthy individuals, show significant associations between dynamic FC within cognitive cerebrocerebellar networks and multiple facets of trait impulsivity, most notably sensation seeking, which is a well-known predisposing factor to AUD (Dick et al., 2010). Together, these findings indicate that dynamic FC, notably within cognitive cerebrocerebellar networks, may have implications for explaining features of the development and maintenance of AUD. So far, however, cerebro-cerebellar dynamics and their potential role in of AUD remain elusive.

In this study, we explored between-group differences in cerebro-cerebellar dynamic FC between a group of AUD patients and a group of unaffected controls, matched to the AUD group on age and sex. Toward this goal, we adopted the sliding window approach (Hindriks et al., 2016) to estimate FC within overlapping segments (L \approx 1 minute) of the BOLD timeseries extracted from a fine-grained map of cerebral and cerebellar regions (Power et al., 2011; Seitzman et al., 2020). With a focus on the temporal variability of cerebro-cerebellar FC, we systematically examined the extent of variation in FC between the cerebellum and the executive control, attention, salience, and default mode networks. Then, we applied a graph theory-based dynamic network analysis, known as multilayer community detection (Braun et al., 2015; Gifford et al., 2020; Mucha et al., 2010), to characterize AUD-related changes in the temporal dynamics of the brain's modular structure. In particular, we quantified the role that the cerebellum plays in these dynamics by estimating diagnostic measures—flexibility and integration—that reflect the tendency of cerebellar regions to communicate with different networks over time and the consistency of their interactions with brain regions from outside their original or "native" functional system (Gerraty et al., 2018; Mattar et al., 2015). In an exploratory analysis, we computed these principal measures at the level of largescale cognitive networks to explore AUD-related changes in their dynamic properties. Our specific hypothesis was that the dynamics of FC within and between the cerebellum and large-scale cognitive networks, especially those anchored in the frontal lobe, would differ between AUD patients and healthy controls, such that AUD would confer an overall reduction in the strength of frontocerebellar FC.

4.2 Methods and Materials

4.2.1 Participants

We acquired high-resolution structural MRI and rsfMRI scans for 18 individuals diagnosed with AUD and 18 age- and gender-matched healthy controls. All participants were free of any serious medical, psychiatric, and neurological disorders at the time of scanning and provided written informed consent to participate in this study, which was conducted with the approval of the Institutional Review Boards of Stanford University and SRI International. Participants received a stipend of \$200 for completing the study. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders was administered to the AUD participants to assess 11 DSM-5 criteria that determine the severity of AUD symptoms (Association, 2013). The severity of AUD—mild, moderate, or severe—is based on the number of criteria met. Demographics and data characteristics are summarized in **Table 4.1**.

4.2.2 MRI Acquisition

For each participant, a single resting-state fMRI scan and cerebrospinal fluid (CSF)nulled Magnetization Prepared Rapid Gradient echo (MPRAGE) T1-weighted scan



FIGURE 4.1: Schematic overview of the main methods used in this study. (A) Whole-brain parcellation using functionally-defined regions of interest with an improved representation of the cerebellum and the subcortex. (B) BOLD signals from all ROIs were segmented into overlapping windows using the tapered sliding window analysis, and a whole-brain FC matrix was constructed by computing pairwise Pearson's correlation in each window. (C) An example FC matrix in an arbitrary time window w_s . The FC profile between distinct brain cognitive networks and the cerebellum is a sub-matrix (shown as boxes marked by black lines) containing the FC weights between its constituent nodes and nodes of the cognitive cerebellum. We calculated the average cosine distance between the FC profiles over all time windows as a measure of temporal variability of cerebro-cerebellar FC. (D) The multilayer modularity quality function $Q(\gamma, \omega)$ was maximized using a greedy Louvain algorithm to detect the optimal community assignment for each brain node in each time window. Using the optimal community structure, we calculated the flexibility of each node as the number of times a node changes its community assignment divided by the total number of possible changes. Also, we calculated the integration of each node as the average probability for a node to be assigned to the same community with nodes outside its native system. Brain networks were visualized with the BrainNet Viewer toolbox http://www.nitrc.org/projects/bnv/. (Xia, Wang, and He, 2013)

	Controls (n=18)	AUD (n=18)	Test	p-value
Gender (male/female)	10/8	13/5	Fisher's exact test	0.49
Age (years)	$48.6 {\pm} 8.81$	53.2±8.76	Two-sample t-test	0.13
Handedness (right/left)	18/0	14/4	Fisher's exact test	0.1
meanFD (mm)	$0.1 {\pm} 0.04$	0.18±0.09	Two-sample t-test	< 0.001
DSM-5 AUD	_	9.58±2.25	_	_

TABLE 4.1: Demographics and Data Characteristics: mean \pm SD

Note: AUD= Alcohol Use Disorder, meanFD= Mean framewise displacement, — no data available.

were acquired. The resting-state scans were acquired with a 1.71 x 1.71 x 3 mm spatial resolution and 200 time-points for each participant. Three protocols associated with slightly different repetition times (TRs) ranging from 2.65 to 2.86 seconds were used during the study. In particular, 28 participants (16 controls, 12 AUD) were scanned with a TR=2.65 s, 4 participants (2 controls, 2 AUD) were scanned with a TR=2.75 s, and 4 participants (4 AUD) were scanned with a TR=2.86 s. Statistical analysis revealed no significant effect of TR on our findings. Therefore, we included the scans from all protocols and did not consider TR as a confounding co-variate in subsequent group comparisons.

4.2.3 Preprocessing

The structural MRI data were preprocessed using *fmriprep* 20.0.1, which is based on Nipype 1.4.1 (Esteban et al., 2019). Briefly, for each participant, the structural high-resolution T1-weighted (T1w) image was corrected for intensity non-uniformity and skull-stripped. Brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) was performed on the brain-extracted T1w using *fast* algorithm implemented in FSL(Jenkinson et al., 2012). Volume-based spatial normalization to the Montreal Neurological Institute (MNI152) standard space was performed through nonlinear registration with *antsRegistration* (ANTs 2.3.1), using the brain-extracted versions of both the T1w image and the MNI152 template. The template selected for spatial normalization was ICBM 152 Nonlinear Asymmetrical

template version 2009c (TemplateFlow ID: MNI152NLin2009cAsym). The transformation parameters for normalization were estimated to be used in the preprocessing of the rsfMRI data.

Preprocessing of rsfMRI data was performed using *fmriprep* 20.0.1, in addition to other custom scripts, and included the following steps: (a) Creation of an EPI reference image using a custom methodology from *fmriprep*; (b) Slice-timing correction using 3dTshift from AFNI; (c) Fieldmap-less susceptibility distortion correction (Huntenburg, 2014; Wang et al., 2017) using a deformation field resulting from coregistering the EPI reference to the same-subject T1w-reference with its intensity inverted using *antsRegistration* algorithm; (d) Head motion correction with respect to the corrected EPI reference using *mcflirt* from FSL to estimate transformation parameters for head motion correction; (e) Coregistration of the corrected EPI reference to the T1w reference image using boundary-based registration from FSL configured with 9 degrees-of-freedom to estimate transformation parameters for coregisration; (f) Resampling the BOLD time series to the output standard space in a single interpolation step by composing all the pertinent transformations (i.e. head motion transform matrices, susceptibility distortion correction, coregistration to T1w image, and normalization to the MNI152 standard space); (g) Reslicing to 222 mm3; (h) Spatial smoothing (FWMH = 4 mm); and (i) Band-pass filtering [0.018Hz-0.1Hz] to attenuate low-frequency drifts and high-frequency noise. The choice of the cutoff frequency for high-pass filtering is consistent with the criterion for choosing a cut-off that attenuates low frequency components below 1/w, where w is the window length, in seconds, in the sliding window analysis (see the section on Dynamic functional connectivity analysis) (Leonardi and Van De Ville, 2015). Finally, nuisance co-variates, including 12 head motion parameters (i.e., six motion parameters and their first-order derivatives), 10 aCompCor principal components from WM, and 10 aCompCor principal components from CSF were regressed from the data in one regression step (Behzadi et al., 2007). The *aCompCor* approach can mitigate head motion effects not accounted for by the 12 motion regressors while also accounting for physiological noise such as respiration and cardiac pulsation (Muschelli et al., 2014). Moreover, the inclusion of more components from *aCompCor* improves the quality of the data and the specificity of FC estimates (Muschelli et al., 2014). The nuisance co-variates were band-pass filtered [0.018Hz-0.1Hz] prior to performing regression to achieve orthogonality between temporal filtering and confounds removal as suggested by Lindquist et al. (2019).

4.2.4 Definition of Brain Functional Networks

To define brain functional networks, we used a set of 300 functionally-defined spherical ROIs positioned around suggested coordinates in MNI space (see Figure 4.1A). The functionally-defined brain parcellation, introduced by Seitzman et al. (2020), is based on the Power-264 cortical atlas (Power et al., 2011) and offers a comprehensive view for the study of brain functional modules and their interactions with improved representations of the cerebellum (27 ROIs) and the subcortex (34 ROIs). The Power-264 cortical atlas was originally created via large-scale metaanalyses of resting-state and task fMRI studies (Power et al., 2011), whereas the recently added cerebellar and subcortical ROIs were defined using a "winner-takesall" partitioning method applied to rsfMRI data and cross-validated across multiple large-scale datasets (Seitzman et al., 2020). Consistent with the study of Seitzman et al. (2020), we partitioned the whole brain into 13 intrinsic functional networks: dorsal sensorimotor network, lateral sensorimotor network, auditory network, visual network, default mode network (DMN), cingulo-opercular network (CON), frontoparietal network (FPN), reward network (RN), salience network (SN), ventral attention network (VAN), dorsal attention network (DAN), parieto-medial network, and medial-temporal network. In this study, however, we focus on and discuss the results related to the dynamics of FC within the cerebellum and between the cerebellum and seven large-scale cognitive networks, namely the DMN, FPN, RN, DAN, VAN, SN, and CON.

4.2.5 Dynamic Functional Connectivity Estimation

We estimated dynamic functional connectivity using tapered sliding window with 50% overlap between windows (see Figure 4.1B). Consistent with previous studies (Damaraju et al., 2014; Fukushima et al., 2018), tapering was done to mitigate the effect of sudden changes associated with the edges of rectangular windows and was

achieved by convolving a rectangular window with a Gaussian of standard deviation $\sigma = 3$ TRs. For the main analysis, we used a window length of 20 time-points for all subjects. This corresponded to 53 seconds, 55 seconds, and 57 seconds for the three scanning protocols with slightly different repetition times, respectively. We chose this particular window length for several reasons. First, shorter windows $(\approx 30 \text{ s or less})$ can capture fast variations in FC but at the expense of introducing spurious FC estimations due to the small number of time-points in each window. Second, longer windows (between 75 s and 100 s) provide more reliable estimates of FC within a single window but are relatively less sensitive to fast variations in FC (Leonardi and Van De Ville, 2015; Telesford et al., 2016). Third, shorter windows help distinguish individual differences in brain network dynamics, whereas longer windows help distinguish the dynamic roles of distinct brain systems in a temporal core-periphery organization, where regions of the core are minimally dynamic and regions in the periphery are maximally dynamic (Mattar et al., 2015; Telesford et al., 2016). Because we were interested in differences between individuals as well as brain systems, we chose a window length of 20 TR as a compromise between shorter and longer windows. Within each window, we constructed a 300×300 FC matrix by computing the pairwise Pearson product-moment correlation coefficient amongst the BOLD time series of all ROIs. Finally, the resulting windowed FC matrices were Fisher r-to-z transformed to stabilize the variance of correlation coefficients. We repeated the same analysis using 15 TR and 25 TR windows to assess the robustness of our results to different choices of window lengths. Moreover, we adopted the multiplication of temporal derivatives (Shine et al., 2015) as an alternative to sliding window correlation to assess the robustness of our findings to different choices of dynamic FC analysis approach. Details and results of the different validation analyses are reported in the Supplementary Material 4.5.

4.2.6 Temporal Variability of Cerebro-Cerebellar FC

A straightforward measure that has been used in previous studies to quantify dynamic FC at the scale of nodes and networks is the temporal variability (Zhang et al., 2016). In this study, we calculated the temporal variability of the FC profiles between cerebral nodes, belonging to any cognitive network of interest, and cerebellar nodes belonging to the cognitive cerebellum (see Figure 4.1C). The cognitive cerebellum included nodes participating in higher-order cognitive networks and mainly located in the posterolateral cerebellum. For a given window *s*, the FC profile between a brain node *i* and the cognitive cerebellum, denoted $FC_{i,s}$, is a connectivity vector containing the FC weights between that node and every node in the cognitive cerebellum. We calculated the temporal variability of FC between a node *i* and the cerebellum, denoted V_i , as the average pairwise *cosine distance* between the FC profiles (i.e., FC vectors) over all windows. Then, we averaged the temporal variability scores over nodes belonging to the same large-scale cognitive network to obtain a network-level measure of the temporal variability of cerebro-cerebellar FC (see Figure 4.1C). We calculated V_i using the following formula:

$$V_i = \frac{2}{T(T-1)} \sum_{s=2}^{T} \sum_{r=1}^{s} \text{cosine distance}(FC_{i,s}, FC_{i,r})$$
(4.1)

where T denotes the total number of windows, $FC_{i,s}$ and $FC_{i,r}$ are the FC profiles between cerebral node *i* and the cognitive cerebellum in windows *s* and *r*, respectively, and *cosine distance* is given by:

cosine distance(
$$FC_{i,s}, FC_{i,r}$$
) = $1 - \frac{FC_{i,s} \cdot FC_{i,r}}{FC_{i,s}FC_{i,r}}$ (4.2)

where the second part of (4.2) represents the cosine similarity, which is a measure of similarity between two vectors in high-dimensional space. The values of cosine similarity vary between -1 and 1, indicating maximal dissimilarity and maximal similarity, respectively. This approach for estimating FC temporal variability was implemented in previous studies using Pearson's correlation instead of cosine similarity (Long et al., 2020; Zhang et al., 2016; Zhu et al., 2019). However, cosine similarity has been shown to provide a better distinction between groups than Pearson's correlation (Cabral et al., 2017; Menon and Krishnamurthy, 2019). Note that we did not compare different measures of similarity (or dissimilarity) as this is beyond the scope of the current study.

4.2.7 Multilayer Modularity Analysis

We applied multilayer community detection to the windowed FC matrices to identify time-varying functional communities that permitted the estimation of diagnostic measures of the dynamic behavior of different brain networks. Particularly, we used the generalized Louvain-like multilayer community detection method (Mucha et al., 2010; Jutla, Jeub, and Mucha, 2011-2019) and implemented it using an opensource code package in Matlab https://github.com/GenLouvain/GenLouvain. The functional communities in each window were identified by maximizing (or optimizing) a multilayer modularity quality function Q, which uses the relative densities of connections within and between communities to assign nodes that have stronger connections than expected in a Newman-Girvan null model to the same functional community (Blondel et al., 2008; Mattar et al., 2015; Mucha et al., 2010; Newman and Girvan, 2004). For each participant, we ran 100 optimizations of the modularity quality function, defined as:

$$Q(\gamma,\omega) = \frac{1}{2\mu} \sum_{i,j,s,r} [(A_{i,j,s} - \gamma_s \frac{k_{i,s} k_{j,s}}{2m_s}) \delta(M_{i,s}, M_{j,s}) + \delta(i,j) \omega_{j,r,s}] \delta(M_{i,s}, M_{j,s})$$
(4.3)

where A_{ijs} represents the adjacency matrix or FC matrix in window s, $\frac{k_{i,s}k_{j,s}}{2m_s}$ is the term associated with the Newman-Girvan null model, $k_{i,s}$ and $k_{j,s}$ are the strengths (or weighted degrees) of nodes i and j in window s, respectively, m_s is the density, or the total sum of weighted degrees, of the graph in window s, μ represents the total sum of weighted degrees across all windows, γ_s is the structural resolution parameter in window s, $\omega_{j,r,s}$ is the inter-layer temporal resolution parameter or the connection strength between node j in window s and itself in window s, respectively, and $M_{j,s}$ are the community assignments of nodes i and j in window s, respectively, and, finally, $\delta(M_{i,s}, M_{j,s})$ is Kronecker's delta equal to 1 when $M_{i,s}=M_{j,s}$ and equal to zero otherwise. Because this multilayer modularity function accepts non-negative adjacency matrices only, we thresholded the windowed FC matrices to remove negatively weighted edges. In addition, we fixed γ and ω to the commonly used value

 $\gamma = \omega = 1$ due to the lack of application-driven justification or consensus for determining the optimal values of these parameters (Betzel et al., 2017; Braun et al., 2015). However, we examined the effects of small variations in the parameters' values by varying both γ and ω over the range [0.95, 1.05] with steps of 0.05 and maximizing the multilayer modularity function for all pairs of parameter values (see results in Supplementary Material). Finally, due to the heuristic nature of the algorithm and the near-degeneracy of the optimization process of the multilayer modularity quality function, different runs of the algorithm may provide slightly different partitions of nodes into communities (Mucha et al., 2010). Therefore, we performed 100 runs of the modularity optimization procedure for each participant and averaged the scores of dynamic network measures over all runs.

4.2.8 Dynamic Network Diagnostics: Flexibility and Integration

Multilayer modularity optimization yields an assignment for each node into a functional community in each window. This permits the quantification of the dynamic reconfiguration of community assignments across regions over time, reflecting the emergence and dissolution of communities as patterns of FC change from one window to another (Bassett et al., 2015; Braun et al., 2015). To measure the dynamic reconfiguration of community assignments in the cerebellum, we calculated the **nodal flexibility** of each cerebellar node. Flexibility reflects how often nodes switch their communities; it is the number of times a node changes its community affiliation across two consecutive windows divided by the total number of possible changes (i.e., total number of windows) (Bassett et al., 2015; Braun et al., 2015), and defined as:

$$f_i = 1 - \frac{1}{T - 1} \sum_{s=1}^{T - 1} \delta(M_{i,s}, M_{i,s+1})$$
(4.4)

where T is the total number of windows, $M_{i,s}$ and $M_{i,s+1}$ are the community assignments of node *i* in two consecutive windows *s* and *s*+1, respectively, and $\delta(M_{i,s}, M_{i,s+1})$ is Kronecker's delta equal to 1 when $M_{i,s}=M_{i,s+1}$ and equal to zero otherwise. The overall cerebellar flexibility for each participant was calculated by averaging the flexibility scores over all cerebellar nodes.

Nodal integration, sometimes called "spatiotemporal diversity" (Chen et al., 2016), is defined as the average probability for a node to be assigned to the same community with nodes from other brain systems across windows (Bassett et al., 2015; Mattar et al., 2015). In this study, intrinsic brain systems were defined according to the 13 consensus network partitions (Seitzman et al., 2020). To calculate integration, we first had to construct the **module allegiance matrix** or the "temporal cooccurrence matrix" for each participant (Chen et al., 2016). The module allegiance matrix summarizes the dynamic community structure and measures the level of synchronisation between the reconfiguration profiles of any two nodes across windows (Chen et al., 2016). Each entry in the module allegiance matrix, denoted $G_{i,i}$, corresponds to the proportion of windows in which any two nodes *i* and *j* are assigned to the same community (Bassett et al., 2015; Braun et al., 2015). A high value of allegiance between two nodes indicates that they are often assigned to the same communities across time windows. Using the module allegiance matrix and the 13 time-averaged consensus network partitions provided by Seitzman et al. (2020), we calculated the average probability for each cerebellar node to be assigned to the same community with nodes outside its native system, defined as:

$$I_i^S = \frac{1}{N - n_S} \sum_{j \notin S} G_{i,j} \tag{4.5}$$

where *S* is the native brain system that node *i* belongs to, *N* is the total number of nodes, n_S is the total number of nodes in brain system *S*, and $G_{i,j}$ is the magnitude of allegiance between node *i* and any node *j* not belonging to system *S*. The total cerebellar integration for each participant was calculated by averaging the integration scores over all cerebellar nodes. Finally, we conducted an exploratory analysis to estimate the average flexibility and integration in each of the seven large-scale cognitive networks.

Network	Controls mean(SD)	AUD mean(SD)	<i>F</i> _{1,31}	p-value (FDR)	η_p^2
DMN	0.76(0.03)	0.77(0.046)	0.14	0.71	0.005
FPN	0.71(0.055)	0.76(0.046)	7.01	0.031	0.18
RN	0.82(0.036)	0.82(0.048)	0.7	0.533	0.02
DAN	0.77(0.04)	0.76(0.07)	0.72	0.533	0.02
VAN	0.79(0.04)	0.82(0.052)	7.34	0.031	0.19
SN	0.8(0.035)	0.82(0.045)	1.28	0.48	0.04
CON	0.8(0.033)	0.81(0.027)	0.93	0.533	0.03

TABLE 4.2: Results of Group Comparisons in Temporal Variability of Cerebro-Cerebellar FC

Note: AUD= Alcohol Use Disorder, SD=Standard Deviation, FDR= False Discovery Rate, F=

F-statistic, η_v^2 = Partial eta-squared effect size, **DMN** = Default Mode Network, **FPN** =

Fronto-Parietal Network, **RN**= Reward Network, **DAN**= Dorsal Attention Network, **VAN**= Ventral Attention Network, **SN**= Salience Network, **CON**= Cingulo-Opercular Network

4.2.9 Statistical Analysis

We used two-sample t-tests to test for differences in age and head motion between groups, and Fisher's exact test to test for differences in gender and handedness distributions between groups. For the main and exploratory analyses, we used univariate analysis of covariance (ANCOVA) to test for differences between groups on temporal variability, flexibility, and integration controlling for the effects of age, gender, and head motion. Moreover, we used ordinary least squares (OLS) regression analysis to test for associations between AUD symptom severity, assessed via the DSM-5 AUD total score, and measures of cerebro-cerebellar dynamic FC that show significant differences between groups, while controlling for age, gender, and head motion. Finally, we used the Benjamini–Hochberg false discovery rate (FDR) procedure to control for the rate of Type-I errors from multiple comparisons at $\alpha = 0.05$ (Benjamini and Hochberg, 1995); however, we did not correct for multiple comparisons in the exploratory analyses.

Score	Controls mean(SD)	AUD mean(SD)	<i>F</i> _{1,31}	p-value (FDR)	η_p^2
Flexibility	0.45(0.033)	0.4(0.06)	8.61	0.031	0.22
Integration	0.28(0.012)	0.3(0.019)	9.11	0.031	0.23

TABLE 4.3: Results of Group Comparisons in Cerebellar Flexibility and Integration

Note: **SD**=Standard Deviation, **FDR**= False Discovery Rate, **F**= F-statistic, η^2 = Partial eta-squared effect size

4.3 Results

4.3.1 Group Comparisons: Temporal Variability of Cerebro-Cerebellar FC

Results of group comparisons showed that, relative to the controls, the AUD group exhibited significantly greater temporal variability of FC between the cerebellum and two large-scale cognitive networks: FPN ($F_{1,31} = 7.01$, p(FDR) = 0.031) and VAN ($F_{1,31} = 7.35$, p(FDR) = 0.031). Group differences were not forthcoming in other networks: DMN ($F_{1,31} = 0.144$, p(FDR) = 0.71), RN ($F_{1,31} = 0.7$, p(FDR) = 0.533), DAN ($F_{1,31} = 0.72$, p(FDR) = 0.533), SN ($F_{1,31} = 1.28$, p(FDR) = 0.48), and CON ($F_{1,31} = 0.93$, p(FDR) = 0.533). Statistical details of group comparisons in temporal variability of cerebro-cerebellar FC are summarized in Table 4.3 and illustrated in Figure 4.2.

4.3.2 Group Comparisons: Cerebellar Flexibility and Integration

Results of group comparisons showed that, on average, the AUD group exhibited significantly less cerebellar flexibility than controls across the fMRI scanning interval ($F_{1,31} = 8.61$, p(FDR) = 0.031), indicating that over time, cerebellar nodes switched their community affiliation less frequently in the AUD group than the controls. By contrast, the AUD group demonstrated significantly greater cerebellar integration than controls across the scanning interval ($F_{1,31} = 9.11$, p(FDR) = 0.031), indicating that over time, cerebellar nodes belonging to diverse brain systems were integrated into functional communities with nodes outside their native system



FIGURE 4.2: (A) Violin plots of temporal variability of FC between the cerebellum and seven large-scale cognitive networks for the AUD group and controls. Asterix show p < 0.05 (FDR corrected) for group differences. (B) Brain plot of the frontoparietal and ventral attention networks. (C) Scatter plot representation of the significant correlation between the temporal variability of VAN-Cerebellum FC and the DSM-5 AUD symptom severity. Brain networks were visualized with the BrainNet Viewer toolbox http://www.nitrc.org/projects/bnv/ (Xia, Wang, and He, 2013). *r*= Correlation coefficient, **p**= FDR-corrected p-value. **HC**= Healthy Controls, **DMN**= Default Mode Network, **FPN**= Fronto-Parietal Network, **RN**= Reward Network, **DAN**= Dorsal Attention Network, **VAN**= Ventral Attention Network, **SN**= Salience Network, **CON**= Cingulo-Opercular Network

more often in the AUD group than in controls. Statistical details of group comparisons in cerebellar flexibility and integration are summarized in Table 4.4 and illustrated in Figures 4.3A and 4.3B, respectively.

4.3.3 Associations with AUD Symptom Severity

Ordinary least-squares regression analysis revealed a significant positive correlation between AUD severity expressed as the total score on DSM-5 and the temporal variability of VAN-Cerebellum FC (R = 0.6, t = 2.9, p(FDR) = 0.031; see Figure 4.2C). We did not observe significant correlations between AUD severity score and the temporal variability of FPN-cerebellum FC (R = -0.08, t = -0.365, p(FDR) = 0.72), cerebellar flexibility (R = 0.11, t = 0.45, p(FDR) = 0.72), and cerebellar integration R = 0.27, t = 1.1, p(FDR) = 0.533).



FIGURE 4.3: Violin plots of (A) cerebellar flexibility and (B) integration for the AUD group and healthy controls (HC). Asterix show p < 0.05 (FDR corrected) for group differences.

4.3.4 Exploratory: Network Flexibility and Integration

Results of group comparisons in the exploratory analysis revealed statistically significant group differences in network flexibility and integration (see Figures 4.4A and 4.4B). Specifically, relative to controls, the AUD group exhibited significantly less flexibility in the SN ($F_{1,31} = 21.6$, p < 0.001 uncorrected) and CON ($F_{1,31} = 6.01$, p = 0.02 uncorrected). Furthermore, relative to controls, the AUD group exhibited significantly greater integration in the FPN ($F_{1,31} = 5.4$, p = 0.026 uncorrected).

 η_p^2 Network Score Controls mean(SD) AUD mean(SD) $F_{1,31}$ p-value SN Flexibility 0.46(0.025)0.4(0.03)21.6 < 0.0010.42 CON 0.02 Flexibility 0.45(0.03)0.42(0.035)6.01 0.15 FPN Integration 0.28(0.013) 0.29(0.017) 5.4 0.026 0.12

TABLE 4.4: Results of Group Comparisons in Network Flexibility and Integration

Note:**SD**=Standard Deviation, **FDR**= False Discovery Rate, **F**= F-statistic, η_p^2 = Partial eta-squared effect size

4.4 Discussion

Previous rsfMRI studies have reported altered cerebro-cerebellar FC in AUD associated with deficits in executive function, memory, and metacognitive abilities. Most, A 0.60



FIGURE 4.4: Violin plots of (A) network flexibility and (B) network integration for the AUD group and controls. Asterix indicate p < 0.05 (uncorrected) for group differences. (C) Brain plots of the Salience and (D) Cingulo-Opercular networks. Brain networks were visualized with the BrainNet Viewer toolbox http://www.nitrc.org/projects/bnv/ (Xia, Wang, and He, 2013)

if not all, of these findings, however, have been based on time-averaged measures of FC that are blind to fast reconfigurations in the brain's network structure. In the present study, we aimed at exploring AUD-related changes in the temporal dynamics of cerebro-cerebellar resting-state FC, for the first time, using sliding window analysis and multilayer community detection. Our findings revealed that, relative to controls, the AUD group exhibited significantly greater temporal variability of FC between the cerebellum and two cognitive networks: FPN and VAN. Moreover, we found that the AUD group showed significantly less flexibility and greater integration in the cerebellum compared with controls. Finally, results from the exploratory analysis revealed that the AUD group exhibited relatively less flexibility in the salience and cingulo-opercular networks and greater integration in the frontoparietal network. Overall, the current study brings new evidence of AUD-related alterations in cerebro-cerebellar dynamics, most notably in the frontocerebellar circuits, complementing existing literature on the adverse effects of prolonged, excessive intake of alcohol on the brain at different spatial and temporal scales.

4.4.1 Hypervariability of Cerebro-Cerebellar FC in AUD

Temporal variability of FC is believed to reflect a general readiness of the brain to reorganize in response to changing attention demands (Braun et al., 2015; Davison et al., 2015; Douw et al., 2016; Fransson, 2005; Zhang et al., 2016). However, previous studies have shown that hypervariability of FC, during rest, is a hall-mark of brain disorders including schizophrenia, bipolar disorder, autism spectrum disorder, Alzheimer's disease, and Parkinson's disease, potentially reflecting a frequent emergence of a state of disconnectivity and disrupted exchange of information among brain regions (Engels et al., 2018; Harlalka et al., 2019; Long et al., 2020; Mash et al., 2019; Zhang et al., 2019; Zhu et al., 2019).

Likewise, our results revealed that, relative to controls, the AUD group exhibited hypervariability of FC between the cerebellum and both the FPN and VAN, suggesting a disorganized FC dynamics and reduced overall connectivity strength within cerebro-cerebellar executive control and attention networks. These networks are involved in top-down cognitive control, working memory, and attention shifting (Marek and Dosenbach, 2018; Sheffield et al., 2015; Vossel, Geng, and Fink, 2014), which have been shown to be impaired in AUD (Le Berre, Fama, and Sullivan, 2017; Le Berre et al., 2019; Oscar-Berman et al., 2014; Sullivan and Pfefferbaum, 2019). Although these networks are anchored in the frontal lobe, the coordinated interaction among distributed brain regions, including the cerebellum, is believed to be a critical component for maintaining efficient cognitive functioning (Weiland et al., 2014). Thus, we hypothesize that the observed hypervariability of cerebrocerebellar FC within these networks would be associated with deficits in executive function and attention, often attributed to the neurotoxic effects of excessive use of alcohol (Sullivan, Harris, and Pfefferbaum, 2010).

4.4.2 Abnormal Cerebellar Flexibility and Integration in AUD

The AUD group showed significantly less cerebellar flexibility than controls. Flexibility has been previously associated with diverse cognitive processes including working memory (Braun et al., 2015), learning (Bassett et al., 2011), attention (Shine et al., 2016), cognitive flexibility, planning, and processing speed (Gifford et al., 2020; Pedersen et al., 2018), supporting its relevance to cognition and behavior. Moreover, studies of brain disorders have reported abnormally higher levels of whole-brain flexibility in patients with schizophrenia and autism, which is thought to reflect temporally less stable, disintegrated, and disordered network dynamics associated with the unique pathophysiology of these disorders (Braun et al., 2016; Gifford et al., 2020; Harlalka et al., 2019).

Given that the cerebellum is implicated in AUD, the relative cerebellar inflexibility during rest in the AUD group is unlikely to indicate more organized cerebrocerebellar network dynamics, but rather increased functional rigidity of cerebellar nodes across time-varying functional modules. This might reflect a compromised capacity of the cerebellum of AUD patients to flexibly adapt to environmental changes that require fast reconfiguration of brain networks. Nonetheless, our interpretation remains speculative and should be further explored in future studies using externally cued cognitive tasks interspersed by epochs of resting-state, which enable a direct assessment of cerebellar flexibility as environmental conditions change.

We also found that the AUD group exhibited significantly greater integration in the cerebellum than controls. The relatively greater cerebellar integration in the AUD group might reflect a compensatory functional remapping (Chanraud et al., 2013), whereby cerebellar regions tend to connect for longer periods with other regions outside their "native" functional systems to promote normal performance on tasks. Recent findings, however, suggest that abnormal cerebellar activity in AUD patients, who are early in abstinence, is unlikely to reflect compensatory re-organization but rather pathological or maladaptive plasticity, especially in the frontal lobe and the cerebellum (Ritz et al., 2019). In this sense, results from our exploratory analysis also revealed significantly greater integration in the FPN in the AUD group compared to controls. As such, we could also interpret greater integration in the cerebellum and the FPN as a signature of pathological, rather than compensatory, functional re-organization. However, this remains an open question for future studies, which should consider exploring this feature of task-evoked dynamics within frontocerebellar networks using executive control tasks.

4.4.3 Exploratory Analysis: Abnormal Network Flexibility and Integration in AUD

Results of the exploratory analysis revealed that the AUD group exhibited relatively less flexibility than controls in the salience network (SN) and the cingulo-opercular network (CON). These networks subtend portions of the anterior cingulate cortex, anterior insula/operculum, supplementary motor area, thalamus, and basal ganglia (see Figures 4.4C and 4.4D), which are highly vulnerable to alcohol-related damage and are purported to take part in the formation of the addiction cycle (Weiland et al., 2014). Of particular importance, the SN is known to be a highly flexible and versatile network that facilitates the antagonistic activity of the DMN and the executive control networks (i.e., FPN and CON), promoting cognitive flexibility (Chen et al., 2016; Nomi et al., 2016; Steimke et al., 2017). Altered dynamics between those networks has been associated with the disruption of shifting from internally to externally focused attention, leading to inefficient cognitive processing (Bolton et al., 2020). Considering this, we hypothesize that altered SN dynamics in AUD would contribute to commonly reported deficits in cognitive control, memory, and reward/motivation processes (Sridharan, Levitin, and Menon, 2008; Chen et al., 2016). Taken together, the findings from this study corroborate those from the literature suggesting selective and far-reaching alterations in major brain systems encompassing the cerebellum, frontal lobe, and the basal forebrain in AUD (Koob and Volkow, 2016; Sullivan and Pfefferbaum, 2005; Sullivan, Harris, and Pfefferbaum, 2010).

4.4.4 Limitations

Several limitations for this study are worth noting. First, major limitations that might affect the reliability of the current findings are the limited sample sizes and number of timepoints (200 timepoints), which might be sub-optimal for dynamic FC analysis. Future studies should validate current findings using larger sample sizes, longer scans, and probably multiple rsfMRI sessions. A second limitation is that the groups were not matched with respect to certain factors listed in Table ??, such as years of education, socioeconomic status, IQ, depressive symptoms, and smoking status. However, the directionality of these group differences is expected based on the typical epidemiology of the AUD group. A third limitation is the lack of detail at the level of the cerebellum and large-scale brain networks. Therefore, for a more comprehensive view, future studies, guided by specific hypotheses, should explore features of dynamic FC at the level of cerebellar sub-modules. Finally, a general limitation regarding the use of the sliding window approach is that there is still no clear consensus on the optimal window length even though extensive efforts have been made to address this issue (Hindriks et al., 2016; Menon and Krishnamurthy, 2019; Savva, Mitsis, and Matsopoulos, 2019; Shakil, Lee, and Keilholz, 2016). Therefore, to assess the robustness of our findings to different window lengths, we repeated the sliding window analysis with 15 TR and 20 TR windows. The results of this supplementary analysis generally supported our main findings, with a few caveats (see Supplementary Material). This is consistent with previous findings suggesting that different choices of window length can induce some variability in the results (Leonardi and Van De Ville, 2015; Gifford et al., 2020). Hence, care needs to be taken when interpreting findings derived from sliding window analysis.

4.5 Conclusion

To the best of our knowledge, this is the first study to bring evidence of altered cerebro-cerebellar dynamic FC in AUD. Our analysis shows that AUD patients exhibit hypervariability in cerebro-cerebellar networks subserving executive control and attention as well as abnormalities in the network role of the cerebellum at fast timescales. Adding to previous findings, our results suggest that AUD confers alterations to cognitive cerebro-cerebellar networks at different temporal and topological scales. Longitudinal studies will be essential for determining whether the features of cerebro-cerebellar dynamic FC are trait characteristics for the development and maintenance of AUD or are state characteristics that may change with sustained sobriety.

Finally, the present findings may provide an impetus for further studies on the dynamic interactions among functional brain networks that subserve executive functioning, cognitive flexibility, and attention and their role in the etiology and pathophysiology of substance use disorders.

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Author Contributions

Majd Abdallah: Study design, data preprocessing, data analysis, writing the manuscript, and visualization. **Natalie M. Zahr**: Grant funding, study design, data collection, data organization, reviewing and editing manuscript. **Manojkumar Saranathan**: Grant funding and study design. **Nicolas Honnorat**: Initial data preprocessing. **Nicolas Farrugia**: Study design, supervision, reviewing and editing the manuscript. **Adolf Pfefferbaum**: Grant funding, mentorship, and study design. **Edith V. Sullivan**: Grant funding, study design, mentorship, reviewing and editing the manuscript. **Sandra Chanraud**: Grant funding, study design, supervision, supervision, data analysis, reviewing and editing the manuscript.

Supplementary Material for Chapter 4

S4.1 Validation Analyses

To evaluate the effect of different analysis strategies on our findings, we conducted supplementary validation analyses that included different window sizes, different multilayer modularity resolution parameters γ and ω , and a different dynamic FC analysis method. Given that dynamic FC estimates may be affected by changes in window length (Leonardi and Van De Ville, 2015), we repeated the analysis different window lengths of 15 TRs (\approx 40 s) and 25 TRs (\approx 70 s). Then, we tested for group differences in cerebro-cerebellar FC temporal variability, flexibility, and integration in each case. In addition, we repeated the multilayer modularity analyses using different values for the free parameters γ and ω , which are commonly fixed $\gamma=\omega=1$. In particular, we examined the effects of small variations in the parameters' values by varying both γ and ω over the range [0.95, 1.05] with steps of 0.05 and maximizing the multilayer modularity quality function for all pairs of parameter values. Finally, we used the multiplication of temporal derivatives (MTD) technique as an alternative to sliding window correlation to evaluate the effects of changing the dynamic connectivity analysis method on group comparisons.

S4.2 Different window lengths: 15 TR and 25 TR

Results obtained using 15 TR (\approx 40 seconds) and 25 TR (\approx 70 seconds) windows revealed qualitatively similar patterns of group differences as those obtained in the main analysis using 20 TR windows, however, with few exceptions. Particularly, we observed significant FC hypervariability between the cerebellum and both the FPN and the VAN in the AUD group when using 25 TR windows. However, when using 15 TR windows, we found significant FC hypervariability between the cerebellum and the FPN only. In addition, we observed significantly less cerebellar flexibility in the AUD group relative to controls when using 15 TR and 25 TR windows. However, while we found significant group differences in network flexibility in the SAN, CON, VAN, and DMN in the case of 15 TR windows, no significant group difference in network flexibility were observed in the case of 25 TR windows. This is consistent with previous studies showing that shorter windows are more sensitive to individual differences in flexibility, whereas longer windows are more sensitive to inter-regional variations, rather than inter-individual differences, in flexibility (Telesford et al., 2016). Finally, while we observed significantly greater cerebellar and FPN integration in the AUD group relative to controls when using 25 TR windows, no significant group differences in cerebellar and FPN integration were detected in the case of 15 TR windows. Results are summarized below in Supplementary Tables S4.1-S4.4 and illustrated in Supplementary Figures S4.1-S4.3. Note that we did not correct for multiple comparisons in the supplementary analysis.

Network	Controls mean(SD)	AUD mean(SD)	F _{1,31}	p-value	η_p^2
DMN	0.81(0.023)	0.82(0.034)	0.02	0.84	< 0.0001
FPN	0.78(0.04)	0.82(0.04)	7.21	0.012	0.19
RN	0.86(0.03)	0.86(0.04)	2.48	0.125	0.07
DAN	0.82(0.04)	0.81(0.07)	0.25	0.62	0.06
VAN	0.84(0.03)	0.85(0.04)	2.55	0.12	0.07
SN	0.84(0.03)	0.85(0.04)	0.74	0.4	0.02
CON	0.85(0.02)	0.85(0.02)	0.15	0.71	0.005

 TABLE S4.1: Group comparisons in cerebro-cerebellar FC temporal variability (15 TR)

Note: **AUD**= Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η_p^2 = Partial eta-squared effect size



FIGURE S4.1: Violin plots of temporal variability of FC between the cerebellum and seven large-scale cognitive networks for the AUD group and controls obtained using **(A)** 15 TR and **(B)** 25 TR windows. Asterix show p < 0.05 (uncorrected) for group differences

Network	Controls mean(SD)	AUD mean(SD)	F _{1,31}	p-value	η_p^2
DMN	0.72(0.04)	0.73(0.06)	0.61	0.44	0.02
FPN	0.66(0.07)	0.71(0.06)	6.18	0.018	0.17
RN	0.79(0.04)	0.79(0.07)	0.29	0.6	0.009
DAN	0.73(0.05)	0.72(0.07)	0.08	0.77	< 0.0001
VAN	0.74(0.04)	0.78(0.06)	7.75	0.009	0.2
SN	0.75(0.04)	0.78(0.06)	0.62	0.43	0.02
CON	0.77(0.04)	0.77(0.03)	0.28	0.6	0.008

TABLE S4.2:	Results of Group	Comparisons	in	Temporal	Variability
	Cerebro-Cer	ebellar FC (25	Τŀ	R)	

Note: **AUD**= Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η_p^2 = Partial eta-squared effect size

TABLE S4.3: Results of Group	Comparisons in	Flexibility	and Integra-
tie	on (15 TR)		

Network	Metric	Controls mean(SD)	AUD mean(SD)	<i>F</i> _{1,31}	p-value	η_p^2
Cerebellum	Flexibility	0.47(0.03)	0.43(0.05)	10.4	0.003	0.25
	Integration	0.28(0.014)	0.29(0.017)	2.7	0.11	0.08
DMN	Flexibility	0.45(0.03)	0.43(0.02)	5.3	0.03	0.14
VAN	Flexibility	0.48(0.03)	0.45(0.035)	11.85	0.002	0.27
SN	Flexibility	0.47(0.025)	0.44(0.035)	10.5	0.003	0.25
CON	Flexibility	0.48(0.02)	0.45(0.03)	13.8	< 0.001	0.3

Note: **AUD** = Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η^2 = Partial eta-squared effect size

TABLE S4.4: Results of Group Comparisons in Flexibility and Integration (**25 TR**)

Network	Metric	Controls mean(SD)	AUD mean(SD)	F _{1,31}	p-value	η_p^2
Cerebellum	Flexibility	0.43(0.04)	0.39(0.07)	11.1	0.002	0.26
	Integration	0.28(0.018)	0.3(0.025)	7.85	0.009	0.2
FPN	Integration	0.28(0.017)	0.3(0.02)	5.2	0.03	0.14

Note: **AUD**= Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η^2 = Partial eta-squared effect size



FIGURE S4.2: Violin plots of cerebellar flexibility and integration for the AUD group and controls obtained using (A), (C) 15 TR and (B), (D) 25 TR windows. Asterix show p < 0.05 (uncorrected) for group differences.



FIGURE S4.3: Violin plots of network flexibility and integration for the AUD group and controls using (A), (C) 15 TR and (B), (D) 25 TR windows. Asterix show p < 0.05 (uncorrected) for group differences

S4.3 Different values for γ and ω

The spatial and temporal resolutions of the multilayer community detection algorithm are controlled by the parameters γ and ω , respectively (Braun et al., 2016; Pedersen et al., 2018; Gifford et al., 2020). Lower/higher values for γ provide fewer/more communities in each layer, whereas lower/higher values for ω give weaker/stronger temporal coupling between a given node and itself in adjacent layers. Despite the importance of the free parameters γ and ω , they are commonly fixed at a *de facto* value of 1. A complete exploration of all combination of parameter values is beyond the scope of this study. Ideally, there needs to be a principled, theory-driven or data-driven approach for selecting the "correct" free parameters in modularity maximization methods. However, this is still missing and most studies examine γ and ω varied over a narrow range.



FIGURE S4.4: Heatmaps of absolute correlation between flexibility scores in different combinations of γ and ω . This was calculated at the level of the cerebellum and seven largescale cognitive networks. The values in parentheses represent the average correlation in each case.

Accordingly, we examined the effects of small variations in the parameters' values by varying both γ and ω over the range [0.95, 1.05] with steps of 0.05 and maximizing the multilayer modularity function for all pairs of parameter values, as was done previously in (Braun et al., 2015; Braun et al., 2016). First, we performed a repeated measures ANOVA using the "combination" as Then, we evaluated the correlation of flexibility and integration scores of each network, including the cerebellum, obtained across different combinations of values of γ and ω . Results showed that flexibility and integration scores across different combinations of values for γ and ω were highly correlated. Particularly, the average correlation for flexibility scores was $r \approx 0.96$ and for integration scores $r \approx 0.82$. Results are illustrated in Supplementary Figures S4.4-S4.5. This indicates that varying γ and ω varied over a narrow range did not alter the findings of the study.



FIGURE S4.5: Heatmaps of absolute correlation between integration scores in different combinations of γ and ω . This was done for the cerebellum and seven large-scale cognitive networks. The values in parentheses represent the average Pearson's correlation in each case.

S4.4 Multiplication of temporal derivatives

The MTD is as an alternative method to sliding window Pearson's correlation that estimates instantaneous FC patterns (Shine et al., 2015; Shine et al., 2016). First, the temporal derivative of each time series is estimated by subtracting the BOLD intensity at time point *t*1 from the intensity at time point *t*. Then, the temporal derivatives of any two time series are multiplied and their product is divided by the product of their respective standard deviations calculated over the entire time course. A positive MTD FC weight indicates that the BOLD signals of two brain regions are 'coupled' in the same direction i.e., they are either both increasing or both decreasing together, whereas a negative MTD FC weight reflects 'anti-coupling' between two brain regions i.e., the BOLD signal in one region increases while the other decreases (Shine et al., 2015). MTD estimates FC on a single data point, making it susceptible to high frequency noise. To overcome this issue, a simple moving average is used to average FC matrices surrounding a point in time within a window of a certain length. In this study, we estimated dynamic FC using the MTD method with a moving average of length equal to 20 TR and performed the same set of analyses and group comparisons as in the main analysis. Results revealed qualitatively similar patterns of group differences to the main analysis in terms of temporal variability of cerebro-cerebellar FC, cerebellar flexibility and integration, and network integration. However, we did not detect significant group differences in terms of network flexibility. Overall, this validation analysis fairly supported the robustness of the main findings to variations in dynamic FC method with few exceptions. Results are summarized below in Supplementary Tables S4.5-S4.6 and illustrated in Supplementary Figures S4.6-S4.8.



FIGURE S4.6: Violin plots of temporal variability of FC between the cerebellum and seven cognitive networks for the AUD group and controls obtained using the MTD method. Asterix show p < 0.05 (uncorrected) for group differences



FIGURE S4.7: Violin plots of cerebellar (A) flexibility and (B) integration for the AUD group and controls obtained using MTD. Asterix show p < 0.05 (uncorrected) for group differences.

Network	Controls mean(SD)	AUD mean(SD)	$F_{1,31}$	p-value	η_p^2
DMN	0.78(0.024)	0.79(0.04)	0.075	0.78	0.002
FPN	0.75(0.04)	0.79(0.04)	11.15	0.002	0.26
RN	0.82(0.025)	0.825(0.05)	0.65	0.43	0.02
DAN	0.795(0.03)	0.79(0.045)	0.3	0.59	0.009
VAN	0.8(0.03)	0.83(0.04)	7.75	0.009	0.2
SN	0.81(0.03)	0.82(0.04)	0.35	0.56	0.01
CON	0.81(0.02)	0.82(0.02)	3.2	0.08	0.09

 TABLE S4.5: Group comparisons in temporal variability of cerebrocerebellar FC (MTD)

Note: **AUD**= Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η_p^2 = Partial eta-squared effect size

TABLE S4.6: Results of Group Comparisons in Flexibility and Integra-
tion (MTD)

Network	Metric	Controls mean(SD)	AUD mean(SD)	F _{1,31}	p-value	η_p^2
Cerebellum	Flexibility	0.095(0.011)	0.11(0.012)	9.26	0.005	0.23
	Integration	0.3(0.011)	0.31(0.018)	5.1	0.03	0.14
FPN	Integration	0.29(0.012)	0.31(0.014)	6.8	0.014	0.18

Note: **AUD**= Alcohol Use Disorder, **SD**=Standard Deviation, **F**= F-statistic, η^2 = Partial eta-squared effect size


FIGURE S4.8: Violin plots of network (A) flexibility and (B) integration for the AUD group and controls obtained using MTD. Asterix show p < 0.05 (uncorrected) for group differences

General Conclusions and Future Perspectives

Summary

Rationale

The past thirty years of studies on the cerebellum have converged to a fundamental finding that the human cerebellum is involved in cognition, with its posterolateral parts mainly communicating with cerebral association networks (Buckner et al., 2011; Buckner, 2013). Functional neuroimaging techniques, especially restingstate functional magnetic resonance imaging (rsfMRI), have enabled neuroscientists to map the complete functional organization of the human cerebellum and provide insights into a wide array of domains to which it contributes (Buckner et al., 2011; Guell et al., 2018; Schmahmann, 2019). The discovery that the cerebellum possesses prominent cognitive zones has far-reaching implications for how we explore its function and also view brain disorders that arise from disruptions in cerebrocerebellar connectivity. In this context, besides delineating the full organizational extent of the cerebellum, resting-state FC have been used to explore the behavioral correlates of cerebro-cerebellar FC and its alterations in brain disorders, notably alcohol use disorder (Chanraud et al., 2011; Moreno-Rius and Miquel, 2017; Sullivan and Pfefferbaum, 2005).

Yet, the majority of rsfMRI studies on the cerebellum have estimated timeaveraged measures of FC, across entire scanning sessions spanning a few minutes. However, growing evidence, motivated by the dynamic nature of the brain, have suggested that resting-state FC, as measured by fMRI, shows noticeable variations over a range of a few seconds that is associated with behavior and not attributable to physiological noise or resampling variability (Calhoun et al., 2014). In fact, these variations seem to be highly structured and fluctuate among a set of metastable FC patterns, known as states, that recur transiently and inter-changeably across time (Vidaurre, Smith, and Woolrich, 2017). Time-varying FC has strong links to electrophysiological FC, cognitive flexibility, creativity, emotion regulation, and personality traits, and has been found to exhibit alterations in a growing number of brain disorders (Lurie et al., 2020; Preti, Bolton, and Ville, 2017). Yet, despite the postulated cerebellar role in coordinating cognitive processes at fast timescales, which confers dynamic patterns of cerebro-cerebellar FC, the cerebellum has been overlooked and/or poorly represented in most studies of dynamic FC. Hence, the behavioral relevance of cerebro-cerebellar FC dynamics remain elusive.

In this thesis, we addressed this question and hypothesized that the dynamics of cerebro-cerebellar FC, during rest, may be behaviorally relevant, capturing aspects of cognition and behavior not accounted for by time-averaged measures of FC, and to exhibit alterations in brain disorders commonly associated with cerebrocerebellar dysfunction, notably alcohol use disorder (AUD). We tested this hypothesis in two separate resting-state fMRI studies that lay special emphasis on the dynamics of cerebro-cerebellar FC happening at fast timescales and their relation to complex traits and disorders, such as impulsivity (first study) and alcohol use disorder (second study).

The First Study

The first study was motivated by a recent hypothesis for a cerebellar involvement in regulating impulsivity based on converging findings from clinical studies and research in animal models (Miquel et al., 2019). In our study, we hypothesized that individual differences in normal impulsivity traits could be associated with the strength and temporal variability of cerebro-cerebellar resting-state FC. We tested this hypothesis by analyzing rsfMRI data and self-report questionnaires of impulsivity collected from a group of 134 healthy young individuals. We delineated 25 cerebral and 14 cerebellar resting-state networks (RSNs) using group independent components analysis (GICA) and modeled the static and dynamic patterns of FC between them using different data-driven methods. Particularly, in the static FC analysis, we estimated FC matrices and computed the total strength of FC between the cerebellum and distinct brain RSNs for each subject. In the dynamic FC analysis, we used hidden Markov modelling (HMM; Vidaurre, Smith, and Woolrich, 2017) to extract subject-specific FC states, each represented by a correlation and a partial correlation matrix, and then used these to compute the overall temporal variability of FC strength between the cerebellum and distinct large-scale RSNs. Finally, we used multivariate general linear models to evaluate the association between cerebro-cerebellar FC and self-reported impulsivity. We found compelling evidence linking multiple facets of impulsivity to both the strength and temporal variability of cerebro-cerebellar resting-state FC. Particularly:

- Results from the static FC analysis revealed that individual scores on the behavioral approach and inhibition systems (BIS/BAS) negatively correlated with the strength of the direct (i.e., partial correlation) FC between the cerebellum and two large-scale networks: the frontal salience network (FSN) and the basal ganglia (BGN), respectively. These results suggest that stronger FSN-Cerebellum FC, during rest, is associated with increased control over goaldirected behaviors, whereas stronger BGN-Cerebellum FC is associated with less sensitivity towards unpleasant/aversive outcomes and hence less activation of avoidance behavior. These findings comport with the existing literature suggesting that the cerebellum engages in the neural circuits underlying the motivational systems that regulate responses towards rewarding and punishment cues (Brunamonti et al., 2014; Miquel et al., 2019; Moulton et al., 2011).
- Results from the dynamic FC analysis revealed that the UPPS-P lack of premeditation scale was inversely associated with the dynamic FC between the cerebellum and two integrative networks: the FSN and the precuneus/posterior cingulate cortex (pCun/PCC) network. Furthermore, results revealed that the UPPS-P sensation seeking scale positively correlated with the dynamic FC between the cerebellum and four networks: the FSN,

pCun/PCC, BGN, and thalamus. These results suggest that the dynamic interactions, during rest, between the cerebellum and highly integrative hub regions, at the interface of top-down cognitive control and bottom-up reward/saliency processes, may serve to adaptively reconfigure attention and actions in response to a change in environmental conditions.

- Our results also suggest that the dynamics of cerebro-cerebellar FC in healthy individuals are behaviorally relevant and may have implications, along with time-averaged measures, in future studies for explaining features of the development and progression of certain brain disorders marked by impulsive symptomatology.
- Overall, the study highlights the utility of complementing time-averaged (i.e., static) measures of FC with time-resolved (i.e., dynamic) FC analysis in furthering current understanding of the neurobiological correlates of complex traits and the functional repertoire of the cerebellum and the cerebro-cerebellar system.

The Second Study

In the second study, we hypothesized that the dynamics of cerebro-cerebellar resting-state FC at short timescales would differ between individuals diagnosed with AUD and unaffected controls, especially in frontocerebellar circuits, which are particularly vulnerable to alcohol-inflicted damage (Chanraud et al., 2013; Sullivan, Harris, and Pfefferbaum, 2010). We tested this hypothesis by examining AUD-related changes in cerebro-cerebellar FC, during rest, from a dynamic FC perspective. In particular, we used sliding window analysis and multilayer community detection to characterize time-varying patterns of FC within and between the cerebellum and seven large-scale cognitive networks. We observed new evidence of aberrant cerebro-cerebellar functional coupling dynamics especially between the cerebellum and networks anchored in the frontal lobe. Particularly:

• We observed evidence of altered cerebellar dynamics across the time-varying functional modular structure in AUD, characterized by hypervariability of FC

between the cerebellum and both the frontoparietal network (FPN) and the ventral attention network (VAN), the latter of which significantly correlated with AUD symptom severity. This is indicative of the presence of aberrant communication dynamics amongst the nodes of the cerebro-cerebellar executive control and attention systems, possibly contributing to a lower overall connectivity within these systems and comporting with previous findings of frontocerebellar dissociation in AUD.

- We also detected altered dynamic modular structure in AUD, characterized by relatively less flexibility and greater integration in the cerebellum of alcoholics compared with controls. The first of which indicates temporal rigidity of cerebellar nodes across time-varying functional modules, potentially reflecting a compromised capacity of the cerebellum to flexibly adapt to environmental changes, which might explain inefficient cognitive processing. The latter finding, along with a finding from the exploratory analysis showing greater integration in the frontoparietal network, might be attributed to either compensatory functional remapping of frontocerebellar circuits or maladaptive plasticity inflicted by excessive use of alcohol. This should be further explored in future studies using cognitive task paradigms.
- The findings from this study extend those from the literature that suggest the presence of selective yet far-reaching alterations in major neural systems encompassing the cerebellum, frontal lobe, basal forebrain, and the limbic system in substance dependence in general, and in particular, alcohol dependence.
- Importantly and foremost, the findings of this study are consistent with previous studies showing altered frontocerebellar FC in AUD patients, which might have future implications for explaining features of the development of cognitive deficits in AUD and improving our understanding of the functional network organization of the brain with addiction.

Future Directions

A sizeable corpus of literature has emerged over the past thirty years focusing the role of the cerebellum in cognitive and affective functions. While the findings of this thesis corroborate and extend the existing literature, they are based on correlative relationships typically derived from resting-state and significance-tested for proof of concept, which precludes making inferences regarding how the cerebellum contributes to cognition and behavior. In fact, most interpretations derived from imaging findings, so far, in terms of how the cerebellum might contribute to cognition are speculative and mainly rest on theoretical accounts, such as the *Universal Cerebellar Transform* and *Dysmetria of Thought*, which in turn are mainly predicated on computational models of sensorimotor control and clinical observations. Moreover, given the nature of resting-state FC and the controversies surrounding time-varying measures of FC, it is definitive that more research is needed to complement current findings and develop a broader perspective of the role of the cerebellum in cognitive functions.

That being said, the central question in cerebellar neuroscience should no longer be whether the cerebellum plays a role in certain cognitive processes, but instead research should now focus on how the cerebellum contributes to these functions in both health and disease. In this context, future multimodal designs based on more refined questions and more naturalistic cognitive task paradigms interspersed by rest epochs will help further explicate the underlying mechanisms that drive cerebro-cerebellar functional coupling dynamics. For instance, this can include task-evoked dynamic FC analysis, that include experimentally imposed and traceable shifts in cognitive state at fast timescales that can be captured by hidden Markov models. Further, it can also include brain stimulation modalities, such as transcranial electrical stimulation (Ali, Sellers, and Fröhlich, 2013), embedded within fMRI experiments, to dynamically modulate activity patterns in the cerebellum, while subjects rest or engage in a cognitive task.

Finally, recent hypotheses of *Multiple Cerebellar Functionality* (Diedrichsen et al., 2019) have emerged, holding that the diversity of structurally similar cerebellar modules suggests that the theory of universal computations may be misguiding

and impeding the progress in cerebellar neuroscience (Sokolov, Miall, and Ivry, 2017). The proponents of this hypothesis argue that there can be a universal umbrella term for cerebellar functioning, but that includes domain-specific computations. However, the substantial evidence of cerebellar anatomical uniformity, general principle of the functional organization of the cerebellum at the group levels (Guell et al., 2018), and the highly individual-specific cerebellar maps (Marek et al., 2018), it might be challenging to disentangle unique computations across cerebellar sub-modules using traditional designs. In this case, as a suggestion, combining the suggested continuous task or transcranial stimulation paradigms with precision functional mapping methods (Gordon et al., 2017; Marek et al., 2018) that estimate subject-specifc functional maps, may be informative about the domain-specific computational models in the cerebellum, if they exist.

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