Brain network alterations in Attention-Deficit and Hyperactivity Disorder: Towards an integrative perspective based on systems neuroscience

by

Luis Marcos Vidal

A dissertation submitted by in partial fulfillment of the requirements for the degree of Doctor of Philosophy in

Biomedical Science and Technology

Universidad Carlos III de Madrid

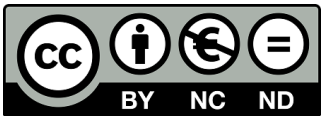
Advisor(s):

Dr. Manuel Desco Menéndez
Dr. Susanna Carmona

Tutor:

Dr. Manuel Desco Menéndez

October 2022



A mis padres y mi hermano.

ACKNOWLEDGEMENTS

Aunque tengo mucho que agradecer a mucha gente, voy a ser breve en los agradecimientos y me voy a referir sobre todo a la gente del ámbito laboral. Esto se debe a que cualquier persona que me conozca sabe que estoy terminando este trabajo a última hora y contrarreloj porque es la única manera en que sé trabajar. Y, por el miedo de querer poner mucho detalle y aún así olvidarme de gente importante, prefiero ser escueto.

Lo primero quiero dar las gracias a La Jefa, Susana Carmona Cañabate porque ha sido mi mentora durante estos años. Ella fue una de las personas que me dieron la oportunidad de empezar en ciencia y luego me apoyó para seguir e intentó (sin mucho éxito) enseñarme a escribir. Y además Susanna ha sido una amiga, con la que me he reído, con la que he discutido y que ha aguantado la vergüenza de mis vitoreos en público. Si Susana fue mi madre adoptiva mis primeros días en el laboratorio, David fue mi padre. A él le debo mis comienzos en el mundo de la programación y mogollón de buenos consejos que creo me han hecho un pelín mejor investigador. También en este sentido tengo que darle las gracias a Chama, que además de ayudarme con mis scripts me enseñó que la gente cool le dice “peinfo”, no “pinfo”. Eso, y grandes expresiones como “se cagó la mula” o “quien ordena mi desorden desordena mi orden” sin las que hoy en día no podría vivir.

De mis compañeros y compañeras actuales qué voy a decir, me han hecho pasar un tiempo magnífico y siempre han estado cuando lo he necesitado. Especialmente quiero darle las gracias a Alberto por su paciencia con mis torpezas informáticas (como borrar todos mis datos del home) y haberme enseñado un montón de cosas. También a Dani, siempre dispuesto a echarte una mano y si te descuidas a hacer tu trabajo, tu cama y limpiarte la casa. Javi, con su incombustible sentido del humor y su amabilidad lo que ha conseguido es transmitirme un poco de su pasión por la ciencia. Y también Magda y María, que siempre han sabido hacer los días de trabajo un poco más divertidos. Por último, quería agradecer a Manolo el haberme dado la oportunidad de trabajar en este laboratorio.

Por supuesto no me quiero olvidar de Jorge Sepulcre por darme la oportunidad de pasar unos meses en su laboratorio, con un ambiente muy acogedor e intelectualmente enriquecedor. Este ambiente se debe también a las grandes personas que trabajan con él, Ibai, Eli y Will, además de Sara, con la que tuve la suerte de coincidir durante nuestra visita.

Finalmente, me siento muy agradecido con la gente que me ha aguantado estos últimos meses sin rechistar. Especialmente a Anto y Borja por acogerme en su casa de El Hierro para mi retiro de escritura, y al resto de gente que ha hecho ese tiempo un poco más llevadero.

PUBLISHED AND SUBMITTED CONTENT

Journal Articles:

- Marcos-Vidal, L., Martínez-García, M., Pretus, C., Garcia-Garcia, D., Martínez, K., Janssen, J., Vilarroya, O., Castellanos, F. X., Desco, M., Sepulcre, J., & Carmona, S. (2018). *Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder.* Human brain mapping, 39(6), 2442–2454. https://doi.org/10.1002/hbm.24013

  This article is wholly included in this dissertation as *Study 2*.

  (Author Contributions: Marcos-Vidal was responsible of processing the data, performing the statistical analysis, creating the plot and conceptualizing and writing the manuscript. Martínez-García was responsible for conceptualizing and writing part of the manuscript and preparing the figures. Carmona was responsible of conceptualizing the content. All authors were involved in writing and reviewing the paper)

- Pretus, C., Marcos-Vidal, L., Martínez-García, M., Picado, M., Ramos-Quiroga, J. A., Richarte, V., Castellanos, F. X., Sepulcre, J., Desco, M., Vilarroya, Ó., & Carmona, S. (2019). *Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder.* Human brain mapping, 40(16), 4645–4656. https://doi.org/10.1002/hbm.24727

  This article is wholly included in this dissertation as *Study 1*.

  (Author Contributions: Pretus was responsible for conceptualizing and writing part of the manuscript and preparing the figures. Marcos-Vidal was responsible of processing the data, performing the statistical analysis, creating the plot and conceptualizing and writing the manuscript. Carmona was responsible of conceptualizing the content. All authors were involved in writing and reviewing the paper)

- Marcos-Vidal, L., Martínez-García, M., Martín de Blas, D., Navas-Sánchez, F. J., Pretus, C., Ramos-Quiroga, J. A., Richarte, V., Vilarroya, Ó., Sepulcre, J., Desco, M., & Carmona, S. (2022). *Local Functional Connectivity as a Parsimonious Explanation of the Main Frameworks for ADHD in Medication-Naïve Adults.* Journal of attention disorders, 10870547221101646. Advance online publication. https://doi.org/10.1177/10870547221101646

  This article is wholly included in this dissertation as *Study 3*.

(Author Contributions: Marcos-Vidal was responsible of processing the data, performing the statistical analysis, creating the plot and conceptualizing and writing the manuscript. Carmona was responsible of conceptualizing the content and preparing the figures. All authors were involved in writing and reviewing the paper)

Posters:

- L. Marcos-Vidal, M. Martínez-García, C. Pretus, D. Garcia-Garcia, K. Martínez, J. Janssen, O. Vilarroya, F.X. Castellanos, M. Desco, J. Sepulcre and S. Carmona. "Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder," presented at the 25th Org. of the HUm. Brain Mapp. (OHBM), Rome, Jun. 2019.

  (Author Contributions: Martínez-García was responsible for conzeptualizing and writing part of the poster and preparing the figures. Carmona was responsible of conceptualizing the content. All authors were involved in writing and reviewing the poster)

Trabajo de Fin de Grado:

- Maestro Aguado, L. (2018). *Local and distant functional connectivity patterns in adults with attention deficit hyperactivity disorder (ADHD).* Degree in Biomedical Engineering, Universidad Carlos III de Madrid. https://e-archivo.uc3m.es/handle/1-0016/29472

OTHER RESEARCH MERITS

Journal Articles:

- S. Carmona *et al.*, "Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes," *Human Brain Mapping*, vol. 40, no. 7, pp. 2143–2152, May 2019. DOI: 10.1002/HBM.24513
- K. Martínez *et al.*, "Sensory-to-Cognitive Systems Integration Is Associated With Clinical Severity in Autism Spectrum Disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 59, no. 3, pp. 422–433, Mar. 2020. DOI: 10.1016/j.jaac.2019.05.033. [Online]. Available: http://www.jaacap.org/article/S0890856719304459/fulltext
- S. Carmona *et al.*, "Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes," *Human Brain Mapping*, vol. 40, no. 7, pp. 2143–2152, May 2019. DOI: 10.1002/HBM.24513
- M. Martínez-García *et al.*, "Do Pregnancy-Induced Brain Changes Reverse? The Brain of a Mother Six Years after Parturition," *Brain Sciences 2021, Vol. 11, Page 168*, vol. 11, no. 2, p. 168, Jan. 2021. DOI: 10.3390/BRAINSCI11020168. [Online]. Available: https://www.mdpi.com/2076-3425/11/2/168/htm%20https://www.mdpi.com/2076-3425/11/2/168
- F. J. Navas-Sánchez *et al.*, "Thalamic atrophy in patients with pure hereditary spastic paraplegia type 4," *Journal of Neurology 2021 268:7*, vol. 268, no. 7, pp. 2429–2440, Jan. 2021. DOI: 10.1007/S00415-020-10387-4. [Online]. Available: https://link.springer.com/article/10.1007/s00415-020-10387-4
- F. J. Navas-Sánchez *et al.*, "Corticospinal tract and motor cortex degeneration in pure hereditary spastic paraparesis type 4 (SPG4)," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 23, no. 1-2, pp. 25–34, Jan. 2022. DOI: 10.1080/21678421.2021.1962353. [Online]. Available: https://www.tandfonline.com/doi/full/10.1080/21678421.2021.1962353
- F. J. Navas-Sánchez *et al.*, "Tract-specific damage at spinal cord level in pure hereditary spastic paraplegia type 4: a diffusion tensor imaging study," *Journal of Neurology 2021 269:6*, vol. 269, no. 6, pp. 3189–3203, Jan. 2022. DOI: 10.1007/S00415-021-10933-8. [Online]. Available: https://link.springer.com/article/10.1007/s00415-021-10933-8
- A. Fernández-Pena *et al.*, "ABLE: Automated Brain Lines Extraction Based on Laplacian Surface Collapse," *Neuroinformatics 2022*, pp. 1–18, Aug. 2022. DOI:

10.1007/S12021-022-09601-7. [Online]. Available: https://link.springer.com/article/10.1007/s12021-022-09601-7

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACRONYMS

ACC Anterior Cingulate Cortex.

ADHD Attention-Deficit and Hyperactivity Disorder.

BOLD Blood Oxygen.

CSF Cerebrospinal Fluid.

dACC dorsal Anterior Cingulate Cortex.

DAN Dorsal Attentional Network.

DFC Distant Functional Connectivity.

DMN Default-mode Network.

FC Functional Connectivity.

FD Framewise Displacement.

fMRI functional Magnetic Resonance Imaging.

FN Functional Network.

FPN Frontoparietal Network.

FWE Familiwise Error.

GM Grey Matter.

GWAS Genetic-Wide Association Studies.

HC Healthy Control.

HRF Hemodynamic Response Function.

IQ Intelligence Quotient.

LFC Local Functional Connectivity.

mPFC medial Prefrontal Cortex.

MRI Magnetic Resonance Imaging.

NA Network Analysis.

ND Neurotypically Developing children.

NYU New York University.

PCC Posterior Cingulate Gyrus.

PU Peking University.

r-fMRI resting-state functional Magnetic Resonance Imaging.

ROI Region Of Interest.

SFC Stepwise Functional Connectivity.

SFG Superior Frontal Gyrus.

SN Sensorimotor Network.

TFCE Threshold-free Cluster Enhancement.

t-fMRI task functional Magnetic Resonance Imaging.

VAN Ventral Attentional Network.

VN Visual Network.

WM White Matter.

SUMMARY

Attention-Deficit and Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders, affecting mainly the school-age population but also having a moderate prevalence rate into adulthood. It is characterized by symptoms of inattention, impulsivity, and hyperactivity improper for the patient's age. However, this age-dependent characterization of ADHD makes the diagnosis such a problematic issue: the maturation rate is different for each child, making the evaluation of what is age-proper a subjective and difficult question. All of this leads to the ubiquitous question of ADHD, namely, whether there is overdiagnosis of the disease or if it even exists. That is why studying the brain is crucial in ADHD, because finding effective biomarkers able to characterize the disease will allow us to diagnose it more accurately.

Magnetic Resonance Imaging (MRI) is one of the most powerful and versatile tools for studying the brain, providing information about both its structure and activity. Traditional MRI studies have focused on analyzing properties of specific brain regions in terms of their shape (e.g., the volume of a structure) or their relation with a cognitive function (e.g., if a structure activates during object recognition), finding multiple alterations in ADHD [8]. However, these widespread regions that present abnormalities are connected between them and with other areas forming the brain network, and their alterations may indeed represent different parts of a more global phenomenon [8, 9].

There are four main neurobiological models that explain ADHD: the maturational lag hypothesis, the dual-pathway model, the Default Mode Network (DMN) interference hypothesis, and multinetwork models. The maturational lag hypothesis is based on ADHD diagnostic criteria and posits that the brain of people with this condition will resemble a younger one [10]. The dual-pathway model proposes two different processing streams for the main symptoms of ADHD: inattention is related to alterations in the corticostriatal executive circuits, while impulsivity/hyperactivity is associated with abnormalities in emotional processing [11, 12]. The DMN interference hypothesis posits that this functional network is not properly suppressed during goal-directed tasks, which is translated into intrusion of inner mental activity [13]. Finally, multinetwork models approach the neurobiology of people with ADHD as an alteration of multiple functional networks [14, 15].

All of these models have received substantial support from neuroimaging studies, which suggests that all of them are correct but incomplete descriptions of the brain profile of people with ADHD. The present dissertation aims to determine whether there is an alteration of the global brain organization in people with ADHD that may underlie the features that characterize the different neurobiological models of the disorder. For that, we will apply two different graph-theory methods based on systems science to the resting-

state functional Magnetic Resonance Imaging data of adults and children with ADHD. The two proposed metrics are Stepwise Functional Connectivity (SFC) and Local and Distant Functional Connectivity (LFC and DFC). The first one measures the integration of information from sensory cortices to areas related to high-order cognitive functions, and in Study 1 [16], it will be applied to a sample of medication-naïve adults with ADHD. LFC and DFC study topological properties with physical distance restrictions, that is, the level of connectivity of each voxel with those around it or those far away. This method will be applied to a sample of children with ADHD in Study 2 [17] and the same sample of adults used in Study 1 in Study 3 [18].

Our results consist of alterations in widespread regions that overlap with most functional networks [19]. Specifically, in adults with ADHD, we observed a decrease in integration in the DMN that locally affects the Posterior Cingulate Cortex and its functional connectivity with the medial Prefrontal Cortex. Additionally, the integration of sensory information in these areas was also found to be reduced in the same sample. The integration of the DMN and its development into cortical hubs is a crucial process in the maturation of the brain [20], which relates this finding with a maturational lag. In both children and adults with ADHD, we also observed a lack of segregation between the DMN, the Ventral Attentional Network, and the Frontoparietal Network in a frontal area of the brain. The developmental trajectory of this area consists of the differentiation of three regions, each of them pertaining to one of these networks [21], and thus, it is a sign of brain immaturity. Also, overconnectivity (lack of segregation) between these networks underlies the DMN interference hypothesis and is indeed a multinetwork alteration [14, 22]. We also found abnormalities in the Visual Network in the form of increased integration of information in these areas while decreased local functional integration of the region, which reflects a behavior more typical of associative than sensory cortices [23, 24]. Finally, local connectivity of sensorimotor cortices presents different maturation trends between ADHD and controls while predicting ADHD symptomatology in all of them.

In conclusion, our results suggest that for understanding ADHD, we cannot focus just on a few areas related to high-order cognitive functions, but the whole brain functional network is compromised. This goes in line with a recent meta-analysis [8] that was unable to find convergence in specific regions abnormalities and proposed an analysis based on network interactions. Altogether, this dissertation reflects the need to approach ADHD from a systems neuroscience perspective that encompasses all the currently available models instead of proposing alternative reductionist ones.

INTRODUCTION

Preface

Attention-Deficit and Hyperactivity Disorder is one of the most common disorders during childhood and adolescence, and it also has a moderate prevalence rate into adulthood. It affects multiple cognitive domains in those who suffer from it and, more importantly, greatly impacts their quality of life. Concerning the difficulties associated with ADHD's diagnosis, scientific findings have highlighted the relevance of neurobiology for understanding this disorder.

Neuroimaging is a powerful technique to explore structural and functional abnormalities in the human brain, finding alterations in multiple, widespread regions in ADHD. These scattered abnormalities, together with the neuropsychological features of ADHD, have led to four different neurobiological models: the dual-pathway model, the maturational lag hypothesis, the DMN interference hypothesis, and multi-network models. They all have found support from multiple studies, thus suggesting different points of view of the same global alteration. Systems neuroscience can offer an integrative alternative where the brain is considered a unitary object in which the interaction between its elements is critical in understanding global phenomena like the mind and its alterations.

The present dissertation aims to determine whether there is an alteration of the global brain organization in people with ADHD that may underlie the features that characterize the different neurobiological models of the disorder. For that, we will apply two different graph-theory methods based on systems science to the resting-state functional Magnetic Resonance Imaging data of adults and children with ADHD. These two methods will explore several properties of the brain's functional organization that have never been explored before in the context of ADHD, which might be determinant to properly understand the findings reported in the different neurobiological models.

This work is organized in the following fashion. The first chapter is an introduction that summarizes the theoretical information necessary for the comprehension and interpretation of the dissertation. The following three chapters consist of three scientific papers that apply the aforementioned graph-theory methods to children and adults with ADHD. The final chapter is a general discussion that integrates these studies in terms of the previous literature and the four neurobiological models of ADHD.

More precisely, the introduction is divided into four sections: *Attention-Deficit and Hyperactivity Disorder*, *Magnetic Resonance Imaging and Functional Connectivity*, *Network Analysis of Brain Functional Organization*, and *Neurobiological models of ADHD*. The first one contains a global overview of ADHD, primarily focusing on scientific con-

troversies and debates. *Section 2* aims to describe neuroimaging tools, especially resting-state functional magnetic resonance imaging, which is the technique used in the studies. The third section is aimed to explain the theoretical bases of complex networks and describe the properties of the brain when considered. Finally, the fourth section will present the four neurobiological models of ADHD.

The subsequent chapters consist of three studies that have been published as scientific articles. Thus, they contain all the technical information about the samples used, the preprocessing and processing of the imaging data, the graph-theory methods, and statistical analysis. Specifically, *Study 1* consists of the application of Stepwise Functional Connectivity to a sample of medication-naïve adults with ADHD; *Study 2* analyzes the Local and Distant Functional Connectivity patterns of children with ADHD; and *Study 3* studies the same metric but in the adult sample of *Study 1*.

Finally, the last chapter is a general discussion of the three previous studies with respect to the literature. It first offers a summary of the main results, as well as how the two metrics analyzed are related between them. Then, there is an interpretation of the results regarding the relationship between adults and children and their points of convergence and divergence. After that, the different results are interpreted under the main neurobiological models of ADHD. Lastly, I will expose some concluding remarks and the conclusions of this work.

1. Attention-Deficit and Hyperactivity Disorder

1.1. Definition

Attention-Deficit and Hyperactivity Disorder (ADHD) is a developmental disorder characterized by levels of inattention, hyperactivity, and impulsivity improper for the patient's age [25]. Inattention refers to the difficulty sustaining focus, mind wandering, and being disorganized and not due to a lack of comprehension. Hyperactivity is defined as excessive motor activity manifested in body movement (e.g., running) and talkativeness. Finally, impulsivity refers to not evaluating the mid-term/long-term consequences of actions that imply an immediate reward. These three characteristics are related to age because their levels tend to diminish along development, making them considered features of a more "childish" behavior.

According to DSM-V diagnostic criteria, at least six symptoms of inattention and/or six of hyperactivity/impulsivity must be present to diagnose ADHD in children (for a complete diagnostic description, see Appendix 1) [25]. These symptoms must persist for at least six months, have to be incompatible with the developmental level, and have to negatively impact social and/or occupational life. In the case of adults (older than 17), just five symptoms of the inattention and/or hyperactivity/impulsivity domains are enough for the diagnosis of ADHD. Depending on the presence of symptoms in one or both of the symptom domains, we can differentiate between inattentive, hyperactive/impulsive, or combined presentations of ADHD. ADHD onsets during childhood, and the symptoms must manifest before the age of 12 for the diagnosis (even in adults). However, although DSM-V does not contemplate an adult onset of the disease, there is a persistence rate from childhood into adulthood of approximately 15% with full diagnosis and 40-60% with partial remission [26]. A difference in adult ADHD compared to children is a notable reduction of hyperactivity symptoms, and they are also more related to restlessness than to motor activity itself.

Evaluation of ADHD for diagnosis is performed by observation, consulting informants who have seen the patient in specific settings (e.g., school/work), and psychometrics (tests). However, the final decision is subjective, especially in what "improper for patient's age" means since there is much variability in the development rate (Section 4.1 will extend this issue). This raises the ubiquitous question of whether there is overdiagnosis in ADHD or not and highlights the importance of finding effective biomarkers able to characterize the disease.

1.2. Epidemiology

ADHD is one of the most common neurodevelopmental disorders, with an estimated prevalence worldwide of 5.29% in children, according to meta-analytic studies [27, 28]. However, there are big discrepancies in prevalence across different studies, starting from

the wide range of estimated prevalence found in the first analysis performed in the 1970s-1980s. Besides this variability, there is a trend of growth in the persistence from those studies until the ones performed two decades later. These inconsistent estimates of prevalence questioned the validity of the diagnosis, objecting that the criteria were so subjective that could vary across cultural environments. It was even proposed that maybe ADHD is just a cultural consequence of Western societies' hyperstimulation, which the pharmaceuticals took advantage of to make a market niche. However, recent meta-analytic studies reflect that the high variability found in previous studies (including the growth trend over time) was due to methodological differences in diagnostic criteria, sources of information, and variations across regions and countries [27, 28]. When unifying these criteria, no significant differences in prevalence were found between different countries of the six continents or across time from 1985 to 2012 [27, 28]. This seemingly anecdotal question highlights the importance of finding reliable biomarkers for the understanding and detection of ADHD.

In adults, the estimated prevalence falls to 2.5% [29], reflecting the aforementioned remission of part of the patients with ADHD. Nevertheless, the number of adult cases is greater than expected by the remission rate, which suggests that some adolescent and adult cases of ADHD do not have an early onset, contradicting the diagnostic criteria of the DSM-V. A recent review supports this hypothesis and points to a revision of the diagnostic criterion of early onset, as well as proposing late-onset ADHD as a new subtype of the disease [30].

1.3. Etiology

The presence of ADHD is related to both genetic and environmental factors, as well as the interaction between them. I will try now to provide an overview of all of these factors, but it is worth noting that it is hard to establish a causal relationship between them and ADHD due to the observational (rather than experimental) nature of the studies and the complexity of the causal process.

1.3.1. Environmental Factors

Numerous environmental exposures have been related to ADHD. One of the most cited relationships with the disorder is intrauterine exposure to tobacco [31], but more recent studies claim that its effects can be explained by confounding genetic factors [32]. However, other pre and perinatal risk factors cannot be explained by genetics, such as prematurity and low birth weight [33, 34]. The relation between these conditions and ADHD may be damage in the basal ganglia and the middle temporal lobe, since these regions are altered in both premature [35] and low birthweight neonates [36] as well as children with ADHD [37].

Regarding postnatal risk factors, exposure to pesticides and pollutants has a long tra-

dition of relation to ADHD [38]. Socioeconomic disadvantage is also associated with ADHD, as shown by a recent meta-analysis [39]. This environmental factor, however, is more an aggregate of conditions than a variable itself, and so its relation with ADHD may be mediated by parental mental health, educational environment, or food quality, among others [40], but most of the studies have observed that the predictive effect of each of them is independent [41]. Nevertheless, as mentioned before, due to the observational nature of environmental etiological studies, it is not easy to completely separate these effects from genetic causes.

1.3.2. Genetic Factors

There is strong evidence of a high heritability in ADHD from the earliest analysis, with initial estimates based on twin studies ranging from 60% to 90% [42, 43]. This type of genetic studies compares the inheritance rate between monozygotic and heterozygotic twins, since the first share 100% of the genome while the latter share approximately 50% as any other siblings. In addition, environmental conditions are similar in both cases, so the differences in heritability should be related to genetic discrepancies. This type of studies suggests that ADHD is a highly heritable condition, but when comparing their results with those of molecular genetic studies, there is a big discrepancy.

Molecular genetic studies examine which parts of the genetic code are related to a condition. The first molecular genetic studies of ADHD involved studying candidate genes selected a priori because they were thought to be related to the disorder's pathophysiology. These studies were focused mainly on those genes related to Dopamine, Serotonin, Noradrenaline, and synaptic properties [42, 44], and they showed that these genes were important in ADHD etiology even if their predictive value was small [45, 46].

Thus, more powerful tools were required to find if other genes (not selected a priori) were related to ADHD, so Genome-Wide Association studies (GWAS) were performed on ADHD. In this type of studies, the whole genome is analyzed to find alleles associated with some specific condition or trait [47]. At first, GWAS on ADHD did not offer promising results probably because huge sample sizes are required [48], but a more recent study has robustly identified 12 loci implicated in ADHD [49]. None of these loci were one of the previous candidates (e.g., dopaminergic or serotonergic genes), and some authors claim that even greater sample sizes are required to detect the small contribution of the thousands of genes that are thought to be involved in ADHD [50]. Furthermore, these risk loci account for 22% of the disorder's heritability [49], which is far from the 70-80% estimated in twin studies [42]. This mismatch highlights the importance of enlarging the sample sizes to detect more genes related to ADHD, as well as carefully focusing on gene-environment interactions.

1.3.3. Gene-environment Interactions

The hypothesis of explaining part of the 50% mismatch between twin studies and molecular genetic studies by gene-environment interaction lies in the fact that twins share both genetics and the environment, which will not happen in a random sample with the same genotype. Sadly, gene-environment interactions is an understudied topic in ADHD [51], and most studies have focused on dopaminergic genes, finding contradictory results [52]. However, the evidence suggests that gene-environment interactions play an essential role in ADHD and that the limitations of this kind of studies (e.g., one gene related to both ADHD and some specific behavior) must be overcome.

1.3.4. ADHD as a Trait

One of the main obstacles for disentangling ADHD's etiology can be the dichotomous conceptualization of the disease. Numerous studies have related the same genetic or environmental risk factors for ADHD with trait levels in the general population [53, 54]. Two studies used GWAS to obtain polygenic risk scores (an individual's liability to a trait or a condition) for manifesting ADHD as a condition and found that these scores predicted ADHD as a trait in healthy population [53, 55]. Moreover, a posterior study suggested that ADHD as a diagnosis and ADHD as a trait share a common genetic background, with an estimated genetic correlation of 0.96 [56]. All in all, ADHD genetically seems more like the extreme of a continuum than a categorical condition, which is similar to the relation between ADHD scores and adverse life outcomes [57].

1.4. Treatment of ADHD

ADHD typically affects various functional domains of the person's life, increasing the risk of adverse outcomes such as physical and mental health impairments, academic failure, unemployment, and legal troubles, among others. [58, 59]. Thus, the final objective of treating ADHD is to reduce or even avoid these adverse outcomes and not just reduce ADHD symptom scores, that is, to improve life quality. Based on this criterion, evaluation of ADHD treatment outcomes has to incorporate ADHD symptom scores, academic/labor and organizational skills, and mental health issues. Now we will summarize the evidence about the effectiveness of different ADHD treatments, which are divided into two groups: pharmacological and non-pharmacological.

1.4.1. Pharmacological

Medication is the primary method to manage ADHD symptoms and, among the available drugs, psychostimulants are the recommended ones by European [60], US [61], and Latin American [62] organizations. Apart from them, there are also non-stimulant medications, such as atomoxetine, but they are much less effective and less used in clinical practice.

Psychostimulant medications include different formulations of amphetamine and methylphenidate and, as mentioned, they are the first-line treatment for ADHD. They were first used in the 1930s and have similar mechanisms of action, increasing catecholaminergic (dopamine and noradrenaline) transmission in which amphetamines are more effective than methylphenidate [63]. Numerous studies suggest an excellent capability of these drugs to reduce ADHD symptoms, but amphetamines' effect is greater than methylphenidate [64–66]. Their side effects are similar and include insomnia, nausea, and appetite suppression but are more prevalent in amphetamines [67]. This difference in side-effects risk is the cause of NICE guidelines recommending, in children and adolescents between 5 and 18 years, to start with methylphenidate and change to amphetamines only if the treatment response is inadequate [60].

Non-psychostimulant medications show lower responses and less effect on ADHD symptoms, and they are mainly used in patients with some incompatibility or poor response to psychostimulants. There are also various non-stimulant medications, including α-2 agonists (guanfacine and clonidine), noradrenaline transport inhibitors, and atomoxetine. All of them show moderate effect sizes in symptom reduction [68, 69], but some of them, like α-2 agonists, can be used as adjuvants to stimulants when they have a poor effect [70].

In summary, medications undoubtedly produce short-term reductions in ADHD symptoms; however, their value is more controversial in terms of reductions in adverse functional outcomes. While there are a few encouraging studies reporting reductions in criminality [71], motor crash vehicles [72], and depression incidence [73] in ADHD population when using medication, there are some meta-analyses that did not find improvements on academic performance, social function, and overall levels of impairment [74–76]. One of the hypotheses underlying these facts is the loss of medication effect due to the interruption of the treatment [77] or the development of tolerance [78].

1.4.2. Non-pharmacological approaches

Medication is not recommended for children under 5 years, and so non-pharmacological approaches are preferred [60], as well as in cases where there is an expressed preference against medication or in the ones of comorbidity that presents an incompatibility with ADHD's medication. These treatments include parental training, neurofeedback, attentional and executive training, and diets; however, contradictory results have been found about their efficacy. On the one hand, the use of this kind of treatments alone does not have an apparent effect on reducing ADHD symptoms, nor with parent training [79], attentional training [80], or neurofeedback [81]. On the other hand, while the combined usage of medication and psycho-social intervention produces the same reduction of ADHD symptoms as medication alone, there is a greater improvement in functional outcomes with the combined treatment [82]. Thus, evidence suggests that medication is needed to reduce ADHD symptoms, allowing psycho-social interventions, which really improve the

functional outcomes and the patient's quality of life [75].

1.5. Neuropsychology

ADHD is related to multiple neuropsychological alterations with wide variability in intensity across different cognitive and emotional domains [15, 83–85]. In this section, we will explain the different theoretical models of ADHD based on cognitive functions that are impaired. However, there is a description of these cognitive functions in Appendix 2.

1.5.1. Theoretical neuropsychological models of ADHD

The next four models are based in ADHD's symptomatology, not in brain features. It is worth note that they are not the neurobiolical ones, although they may coincide like in the case of the Dual-Pathway Model.

- **Altered Executive Functions**: The first theoretical models for ADHD etiology postulated that the alterations observed were due to deficits in executive functions. Executive functions are kind of the control tower of the brain, and include multiple cognitive processes such as working memory, top-down attention, or response inhibition among others. This first model relied on the similarity between ADHD symptoms and those of patients with frontal lobe lesions, an area of the brain tightly related to executive functions [86]. Among all executive functions, the ones that better differentiate healthy controls from people with ADHD are sustained attention, working memory, and response inhibition [84].

- **Response Inhibition**: Since the different executive functions are interrelated and if one of them is compromised various will be affected, Barkley proposed response inhibition as the central deficit in ADHD [87]. This is probably the most cited theoretical model aiming to explain ADHD and derives the different alterations as a consequence of the deficits in response inhibition. Sustained attention is affected because the subject cannot suppress the competing stimuli that appear. They are also unable to inhibit emotional responses and, thus, perform proper emotional regulation, and it also affects working memory by difficulting keeping information in conscious awareness. Despite being one of the most famous models, a recent umbrella meta-analysis (meta-meta-analysis) found evidence that the effect size of the deficit in response inhibition is not the greatest among the functions disrupted in ADHD [88].

- **Reward-Motivation**: However, all ADHD symptoms could not be explained by deficits in executive functions (even less by response inhibition alone) and so models that incorporate alterations in reward/motivation were proposed [11, 12]. These models come from temporal discounting, a construct that reflects how the subjective

value of a reward decays with time. In the case of people with ADHD, this temporal discounting is steeper than in healthy controls, and they are over-responsive to immediate rewards [89]. These alterations in reward perception may cause impulsivity and are also related to deficits in the frontal lobe, as will be seen in Section 4.2 of the Introduction. Thus, reward-motivation deficits may explain poor academic performance in that it involves long-term rewards, while they can do activities where there are constant short-term rewards [90] for hours (like sports or video games).

- **Dual-Pathway**: There are also models that have focused on the different presentations of ADHD, namely, inattentive and combined inattentive-hyperactive/impulsive. One hypothesis posits that the inattentive subtype is more related to working memory deficits while the combined's central deficit is response inhibition [91]. Another popular model relates inattention with a "cool" processing pathway and hyperactivity/impulsivity with a "hot" processing pathway [15]. By "cool" pathway, the authors refer to emotion-free processing, that is, abstract tasks that involve sustained attention or response inhibition. The "hot" pathway, by its part, is defined as the functions modulating affective tasks, which usually require dealing with reward/motivational responses. All in all, this model relates the inattentive symptoms with executive functions and hyperactivity/impulsivity with reward-motivational functions, which will have its neural correlate in the dual-pathway model (Section sec:DualPathway).

1.5.2. Summay

As it can be seen, the only clear thing about ADHD neuropsychology is that it affects multiple functions, and this is reflected in global measures in this population, such as a low intellectual quotient [92]. This seems reasonable since separating the mind into different functions is more a theoretical conceptualization than a real modularization; all of these functions depend on each other and are remarkably interrelated. In fact, as will be seen in Section 4, neurobiological models of ADHD started involving a few segregated brain regions, and they ended up analyzing the brain as a whole, which is more reasonable in both psychological and biological terms.

2. Magnetic Resonance Imaging and Functional Connectivity

With recent advances in medical imaging techniques such as Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET), we have been able to characterize brain structure and function. Moreover, it has helped us understand how the brain is related to the mind and different cognitive functions, thus obtaining differential patterns in brain disease. From all the neural features available using neuroimaging techniques, Functional Connectivity (FC) has gained particular relevance during the last years [93]. This measure, which allows disentangling the functional organization of the brain, can be obtained using (among others) a special design of functional MRI (fMRI) called resting-state functional MRI (r-fMRI). In this section, we will first explain the basic principles of MRI, how they lead to r-fMRI, and finally both biological and mathematical definitions of FC.

2.1. Magnetic Resonance Imaging

MRI is a noninvasive medical imaging technique that allows obtaining volumetric (3D) images with information about the different tissues or chemical elements of the body. It is based on a phenomenon called Nuclear Magnetic Resonance, described for the first time in 1946 by the Nobel Prize winners Bloch and Purcell. To summarize, MRI is based on the magnetic properties of the different tissues or molecules to obtain images of a part of the body, which is the brain in the case of neuroimaging. It allows differentiation of different tissues, detection of axonal bundles by the direction of movement of the water, or measuring the metabolic consumption by the rate of oxygen (for a more detailed description of MRI physics, refer to Grover *et al.* [94]). However, independently of the MRI modality, the image consists of a volume of voxels (volume elements), which is like a cube composed of smaller ones, each containing a value of the magnetic property measured (Figure 1).

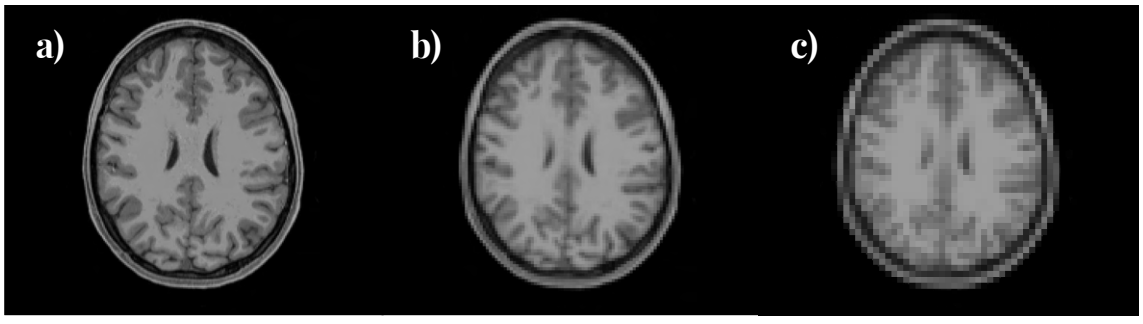


Figure 1: Visualization of a slice of a T1-weighted MRI with different resolutions and, thus, voxel sizes. In a) the voxel size is 1x1x1 mm, in b) the voxel size is 2x2x2 mm, and in c) the voxel size is 4x4x4 mm, where voxels are clearly differentiated.

The T1-weighted and T2-weighted contrasts are the main ways to obtain brain anatomical information. They are kind of a negative one of another, being the T1 more commonly used, which shows the White Matter (WM) brighter than the Gray Matter (GM), being the Cerebrospinal Fluid (CSF) the darkest. The T2 contrast, as mentioned, has the inverse pattern of intensity (Figure 2). With these image modalities, we can obtain information on both GM and WM volume, and with more advanced processing we can get more morphometric information like the cortical thickness, cortical surface area, gyrification index, the width of brain sulci... Nevertheless, the utility of the structural images is not limited to the morphological metrics they provide. It extends to the division of the cortex into multiple regions or the obtention of the different brain tissues, which can then be used to analyze other modalities that do not contain this much anatomical information (e.g., fMRI).

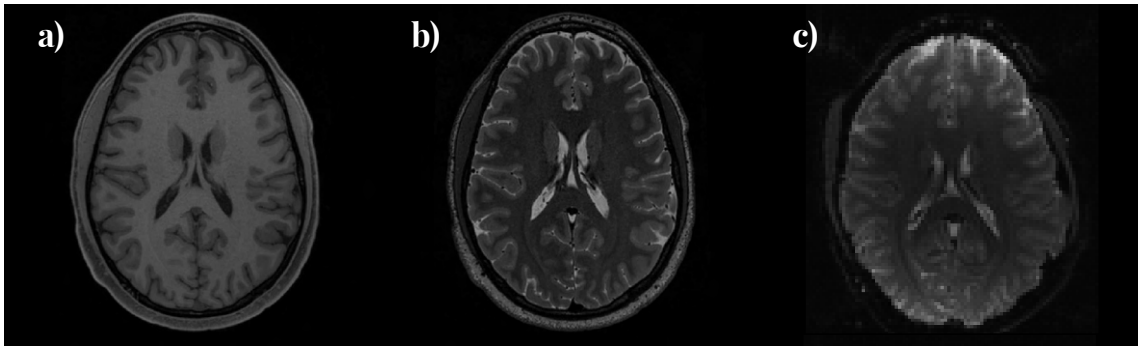


Figure 2: Visualization of different MRI modalities: In a) there is a T1-weighted image, in b) a T2-weighted image, and in c) a T2* image.

2.2. Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) is based on a series of volumes with a contrast called T2* (as seen in Figure 2), which is particularly sensitive to oxygen concentrations in blood. This happens because oxygen is transported by hemoglobin and its form without oxygen (deoxyhemoglobin) is paramagnetic, while the one carrying oxygen (oxyhemoglobin) is diamagnetic [95]. Thus, fMRI signal increases as deoxyhemoglobin levels decrease and there is a greater concentration of oxyhemoglobin, which is why fMRI signal is called blood-oxygen-level-dependent (BOLD) signal. It is considered a measure of functional activity because as the synaptic activity of a group of neurons increases they consume the oxygen in the arterioles around (making T2* signal decrease), but just as this happens the blood flow of that area greatly increases with oxyhemoglobin to cover neuron's requirements (making T2* signal to increase), a pattern called Hemodynamic Response Function (HRF; Figure 3). It is important to note that this is a "long" process (starts 500 ms after onset and peaks after 3–5 s) compared to synaptic timing, so BOLD signal measures the metabolic consumption related to thousands of synapses during this time. Traditionally, it has been assumed that an increase in some brain region's activity

will imply a proportional increase in BOLD signal [96], and, for the sake of simplicity, it is how it will be interpreted in these work even if the nature of BOLD signal is still poorly understood [97–99]. In summary, fMRI allows us to indirectly measure the functional activity of each part of the brain based on its metabolic consumption, and now we will describe how we can analyze this information.

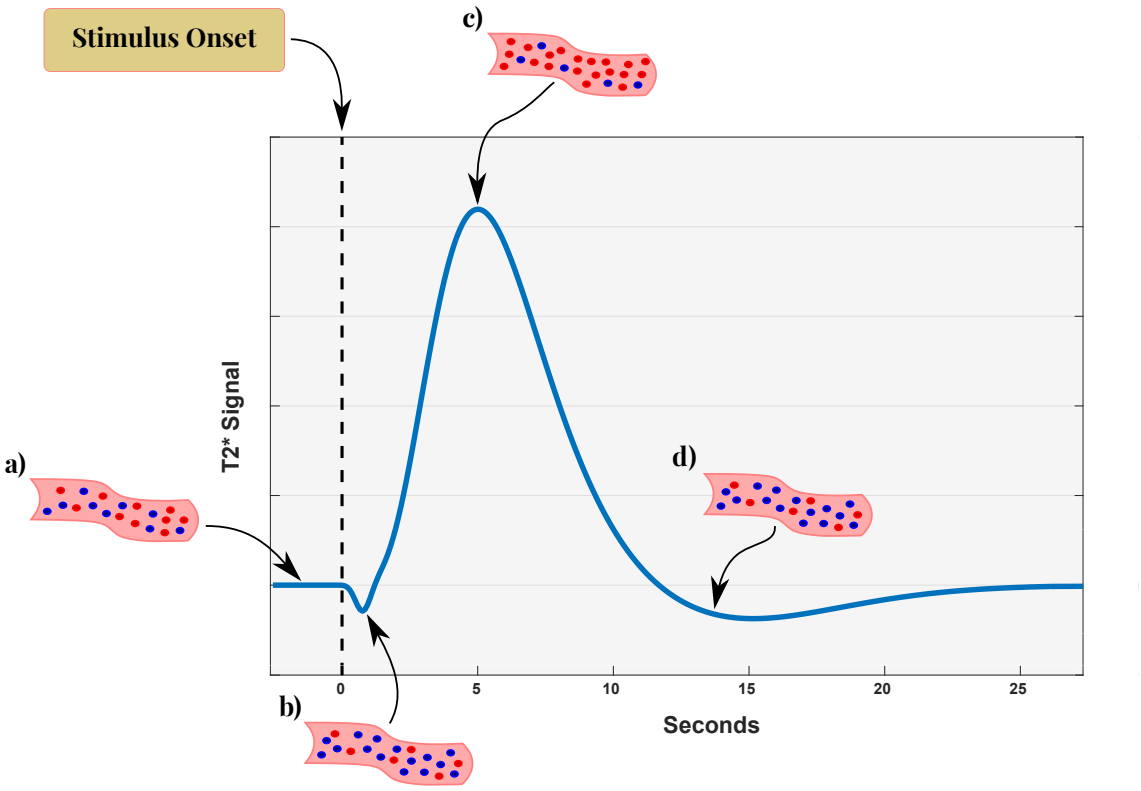


Figure 3: Representation of the Hemodynamic response function biologically and the expected signal obtained in r-fMRI. The red dots represent oxyhemoglobin while the blue dots represent deoxyhemoglobin. a) In normal circumstances, the concentration of the two substances is relatively even, but b) after the stimulus onset the recruited area of the brain rapidly consumes the available oxygen and the concentration of deoxyhemoglobin is greater, producing a decay in T2* signal. c) In response, there is a dilation of the surrounding blood vessels and more oxyhemoglobin gets to the area, producing an increase in T2* signal. d) Finally, an increase in deoxyhemoglobin again produces a decay in T2* signal known as undershoot.

2.2.1. Task-based functional Magnetic Resonance Imaging

The most straightforward use of fMRI is to see in which areas of the brain the BOLD signal (activity) increases during a behavioral task (e.g., finger tapping) which is called task-based fMRI (t-fMRI)[100]. The most straightforward experimental design for a t-fMRI study is called event-related or single-trial paradigm and consists of presenting a single stimulus at a time and trying to see in which areas the BOLD signal behaves as the HRF right at the stimulus' time [101]. However, event-related designs lack the necessary statistical power to detect the subtle differences in BOLD signal, and thus, block

designs were developed. In this paradigm, chunks of resting time are interspersed with chunks of time where the stimulus is present (e.g., six repetitions of 30 seconds of rest followed by 30 seconds of finger tapping)[101]. In block designs, the HRF is supposed to "accumulate" during the stimulus exposition block, so it has more statistical power to detect differences [102]. The two experimental paradigms are depicted in Figure 4 for an illustrative example.

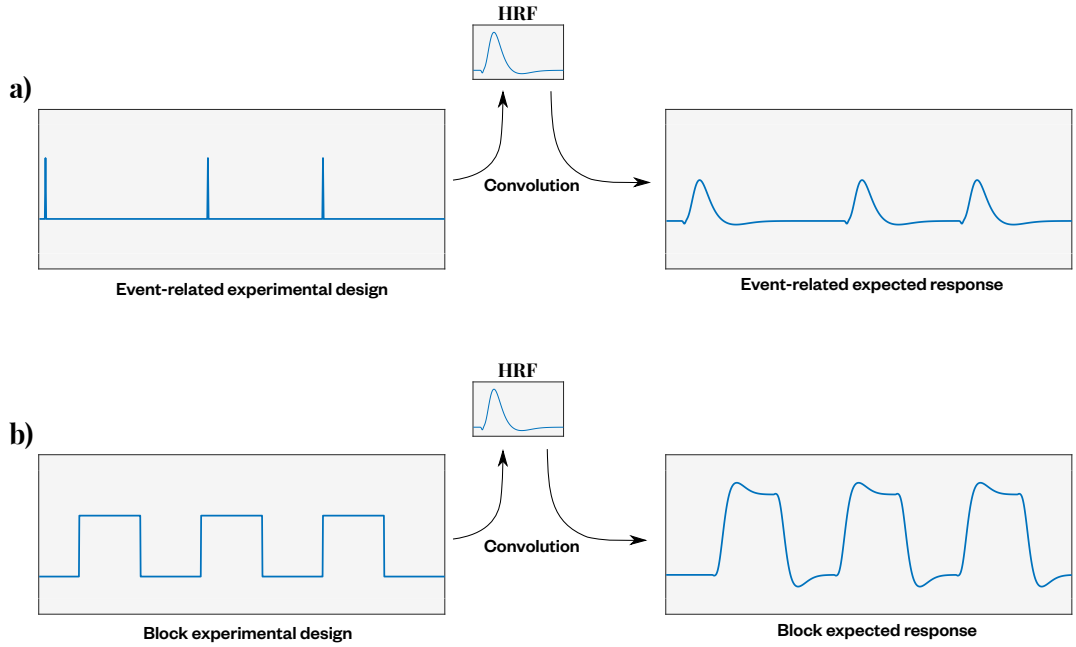


Figure 4: Representation of different experimental designs for t-fMRI and their expected BOLD signal. In a) there is a block design and its expected BOLD, and in b) there is an event-related design and its predicted BOLD signal.

2.2.2. Resting-state functional Magnetic Resonance Imaging

Traditionally, the functional activity that was not related to the task (observed in all the brain but the regions engaged in the task) was thought to represent just physiological noise, and the same applied to the functional activity detected during rest (when the subject is "doing nothing"). However, in Biswal *et al.* [103] and colleagues questioned this assumption and studied the functional activity of the motor cortex in the resting human brain. The results of these analyses were striking, namely, that the BOLD signals of the different parts of the motor cortex were synchronized [103, 104]. This phenomenon was named FC and it is defined as the synchronization of functional activity between different brain regions. The biological meaning of FC was hypothesized by the psychologist David Hebb as "neurons that fire together, wire together", which means that neurons that tend to be involved in the same cognitive activities also present similar patterns of activity at rest. Thus, r-fMRI was born, a modality of fMRI in which the experimental design consists in telling the subject to close his/her eyes and avoid repetitive thoughts [105].

2.3. Functional Connectivity Analysis

Functional Connectivity (FC) is the most widely studied property computed with r-fMRI. If its biological definition is synchronization of activity, the mathematical definition of FC metrics must be a similarity measure. There are multiple statistical tools to measure the level of association between two variables based on their likeness, but the most common and widely used measure of FC is Pearson's correlation r [106]. This statistic ranges from -1 to 1, with 1 representing the exact same signals (or proportional ones), -1 exact opposite signals (or proportional opposite ones), and 0 completely non-related signals. In Figure 5, there is an overview of an example of the computation of two voxel's FC under different scenarios. However, once we have the FC metric, there are several ways of using it to obtain information from the brain. The simplest one uses Regions Of Interest (ROI) and is called ROI-to-ROI analysis, consisting of measuring the FC between two predefined brain regions. Since we define the ROIs a priori, it is important that we need to have previous information on which regions we want to focus on. Another popular way of analyzing FC is by a Seed Analysis, which consists of selecting an ROI and computing its FC with every voxel in the brain, obtaining a map of the connectivity pattern of the aforementioned ROI. Finally, another way of analyzing the FC as measured by Pearson's correlation R is to compute a Connectivity Matrix (CM), which is the FC of every voxel with any other voxel (or dividing the brain into regions and compute the FC between each pair of them) in the brain. That CM will represent a graph and thus, allows us to obtain information about Functional Networks (FNs), which will be the main topic in Section 3.

Although Pearson's correlation is the most widely used method to assess FC, it is not the only way of doing it. For example, various alternative mathematical metrics are available for quantifying the FC between two units (like voxels or ROIs): mutual information, Spearman's correlation, coherence, and phase locking value [106, 107]. Apart from them, there are other ways to analyze r-fMRI data, like Independent Component Analysis, which decomposes all voxels' BOLD signals into a small number of spatiotemporal components, each containing the information of a group of voxels. Thus, these components may be seen as FN, which are groups of regions with similar temporal patterns (or synchronized functional activity). In summary, FC is the analysis of brain functional organization in contrast to the information obtained from t-fMRI, which is more focused on the local properties of the different regions. However, even if both approaches have proved useful during the past decades, the latter has led to inadequate interpretations of the brain, as explained in the next section.

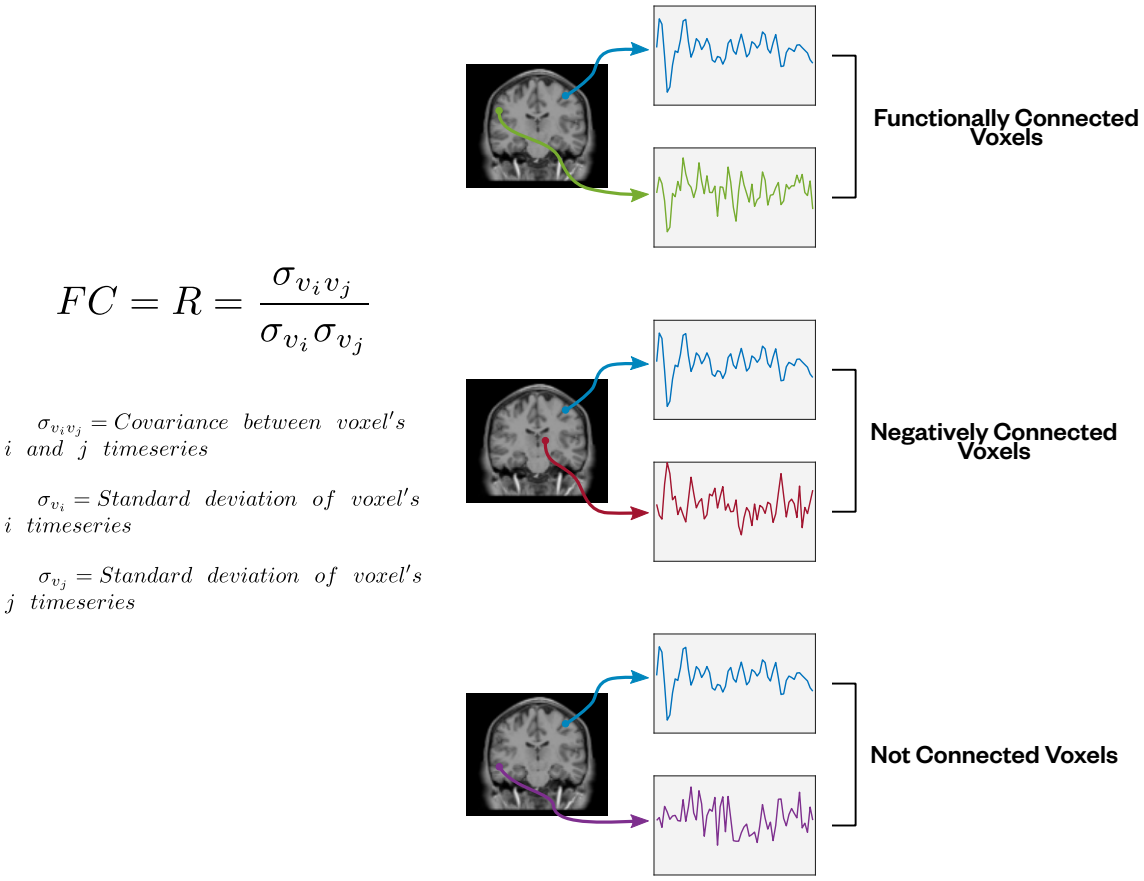


Figure 5: Illustrative example of the computation of FC between two voxels under different connectivity scenarios. FC: Functional Connectivity; *r*: Pearson's correlation coefficient.

3. Network Analysis of Brain Functional Organization

A network is an informal concept that describes an object composed of elements and the interactions between them. We have known that the brain is a set of interconnected units (neurons) since the works of Santiago Ramón y Cajal in the 19th century [108], and thus, it perfectly adjusts to the definition of a network. From a Network Analysis (NA) perspective we analyze MRI data relationally, that is, the properties of study are the relationships (e.g., FC) between the units of study (e.g., voxels). This approach is founded on relational theory (whose origin is explained in Appendix 3) and is operationalized with Graph Theory, being these two theoretical frameworks the philosophical and mathematical foundations of NA. In this section, I will first explain complex systems and how they can change the way we analyze and interpret the brain. Then, I will perform an introduction to Graph Theory and NA and, finally, I will offer a conceptualization of the brain as a complex network and its properties.

3.1. Network Analysis and Complex Systems

Systems and networks are similar concepts that refer to groups of interrelated elements [109]. To understand these concepts and their impact in our conception of the brain, we have to trace the origin of systems science and the paradigm shift it brought about in opposition to reductionism. The "traditional" scientific paradigm is a direct descendant of René Descartes' thought and his view of the world in three main aspects: 1) the elements of study must be as simple as possible, 2) the properties of the elements are inherent to them and independent of the rest of elements and 3) relationships between elements occur in a two-element fashion as if it were a matter of collisions [110–112]. These three characteristics formed the base of modern science leading to scientific frameworks such as Newton's laws of mechanics or the atomic theories, among others. However, as scientific knowledge increased and scientists looked for the link between different scales of observation, the reductionist paradigm began to prove insufficient. This problem was exemplified in the 19th century by John Stuart Mill, who stated that while a molecule of water is composed of atoms of hydrogen and oxygen, no trace of the properties of these two substances was found in the water [113]. Likewise, Mill remarked the difficulty of deriving the properties of a living body from its components [113], a problem that in the 20th century impulsed Ludwig von Bertalanffy to create the General Systems Theory [114], a pioneer theory of Systems Science.

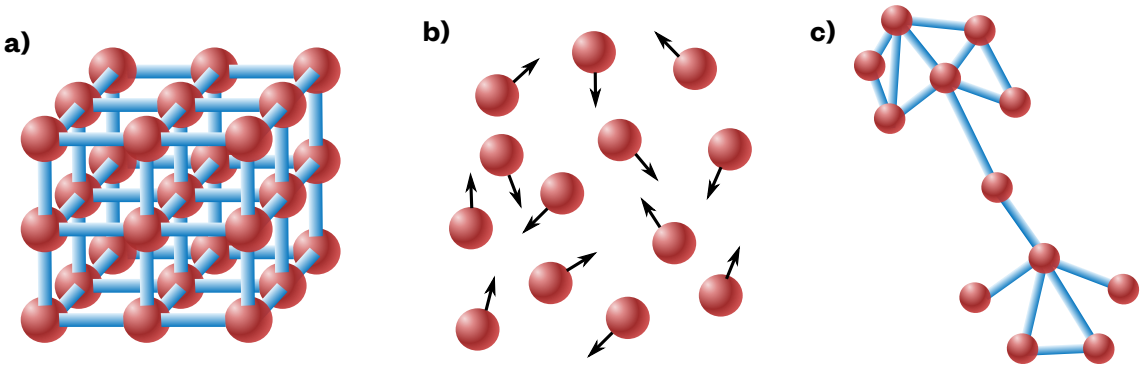


Figure 6: Representation of different systems. In a) there is a coherent system with low complexity at all scales, in b) there is a random system that presents very high complexity at low scale but no complexity at big scale, and in c) there is a complex system with high complexity at different scales of observation.

Systems Science is a transdisciplinar branch of knowledge that studies phenomena from a holistic perspective, namely, that the properties of objects cannot be inferred from the ones of its constituent elements. Thus, a system is defined as a group of interrelated elements that form a whole in an environment [115] and can be simple or complex (as represented in Figure 6). The brain is an example of a complex system because it presents a high level of complexity (number of possible behaviors) at different scales of observation [116]. If we examine the brain at an atomic scale, the constant amount of chemical reactions and great-scale actions are related to multiple rearrangements of the atoms and,

thus, some complexity. If we increase the scale to a cellular level, again we can find a variety of behaviors since, for instance, synapses are producing changes in neurotransmitter concentrations. If we increase even more the scale we can find changes in neuron density, its disposition in the cortex, the level of activity of the neurons or blood flow and, thus, we can consider the brain as a complex system and analyze it as a whole object of interrelated components instead of an aggregate of independent units that may collide.

The pairwise interactions between the elements of a system can be represented in a network [117], and complex networks (which represent complex systems) present particular behaviors different from those of coherent or random systems, as depicted in Figure 6 [116]. Network Analysis, thus, describes the elements in terms of their relationships with the rest of the elements and analyzes the structure of these relationships. In the case of the brain, the elements can be examined at different scales such as neurons, MRI voxels, or whole regions of the brain. Apart from these different scales, we can define the relationships to construct the network as, for example, the euclidean distance between the elements, the number of dendrites connecting them, or their FC.

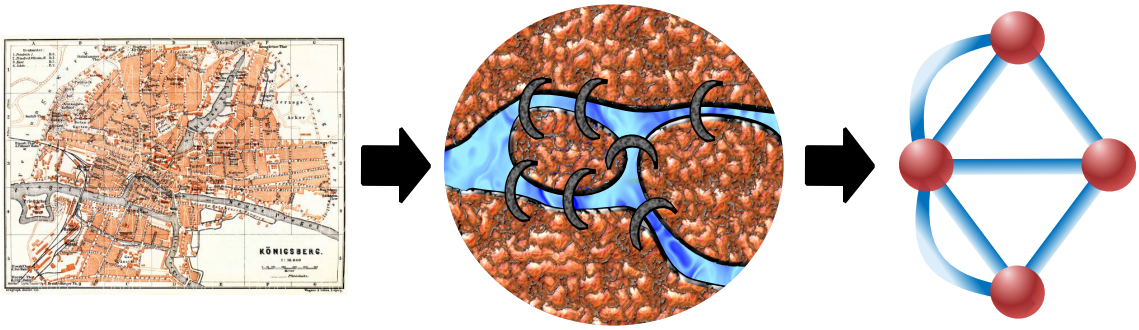


Figure 7: Representation of The seven bridges of Königsberg problem and its transition from a "real world" description of the problem in the form of a map of the city to a schematic representation and finally building an abstract representation in the form of a graph.

3.2. Mathematical foundations of Network Analysis: Graph Theory

If Leibniz is the father of the philosophical foundations of NA, Euler is the father of their mathematical formalization. Leonhard Euler was a Swiss mathematician (among other things) who founded Graph Theory as the mathematical formalization of networks. He faced a problem called The seven bridges of Königsberg (Figure 7) that helped him develop the concept of Graph [118]. A graph is an abstract object defined as a set of vertices or nodes and a set of edges, which are the relationships between the nodes. Mathematically, we can define it as:

Then, what we choose as nodes or edges depends on the object of analysis, but in this dissertation, we will use voxels as nodes and FC as edges. Another mathematical representation of a graph is an adjacency matrix, which is a matrix that represents the

relations between the elements of a network, like in the example of Figure 8. Usually, this adjacency matrix (which can be a CM) is the object used to operate on the graph and to compute network metrics. Once the graph is constructed, multiple organizational properties can be studied for each node, for subgraphs of the network, or the whole graph. These metrics analyze the space generated in the graph, which is called topological space. In Figure 9, the most used metrics are summarized and graphically and mathematically described, but more information on Graph Theory and its multiple metrics can be found elsewhere [119].

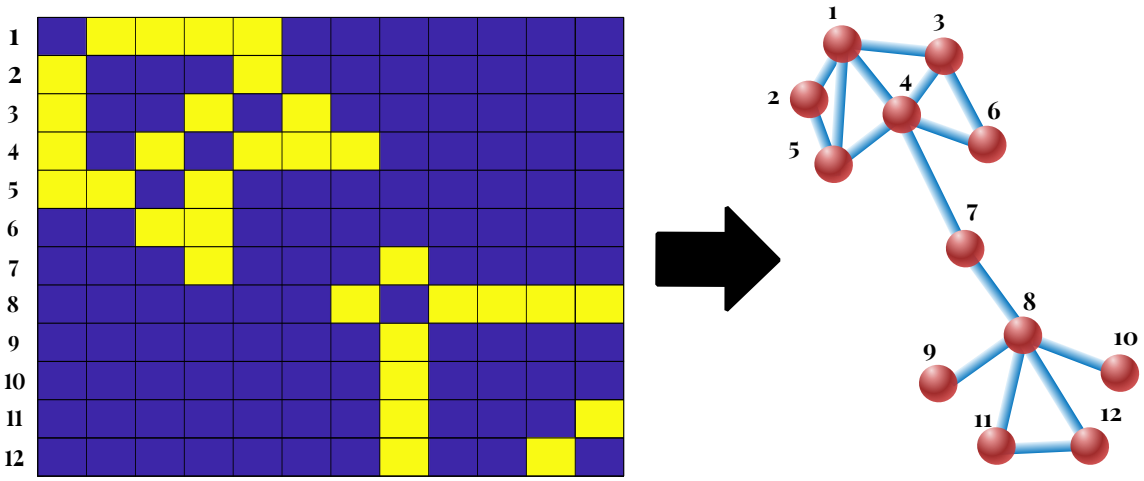


Figure 8: Representation of an adjacency matrix and its graphical representation in the form of a graph. This adjacency matrix is binary (yellow represents 1 and blue 0) and symmetric, giving rise to an undirected and unweighted graph.

There are various types of graphs based on the types of edges they have. The edges can reflect the direction of the relationship, that is, there is a link if the information goes from node a to node b and another if the information goes from node b to a. These types of graphs are called directed graphs, in contrast to undirected graphs in which nodes a and b are just connected between them. Another distinction of the edges is in terms of their strength, where we can find weighted graphs if the edges have a quantitative value or unweighted (or binary) graphs if there is just the presence or absence of the edge. Recent interest in network analysis has led to the analysis of multilayer networks, in which there can be multiple edges between nodes a and b, each reflecting different relational measures [120]. If these multilayer networks are a generalization of traditional graphs in terms of the number of links between two edges, hypergraphs are the generalization of graphs in terms of the number of elements that an edge connects [121]. That means that in hypergraphs, an edge can reflect the interaction between more than two nodes. However, due to the difficulty in analyzing generalized graphs, they are barely used to study brain imaging data [122].

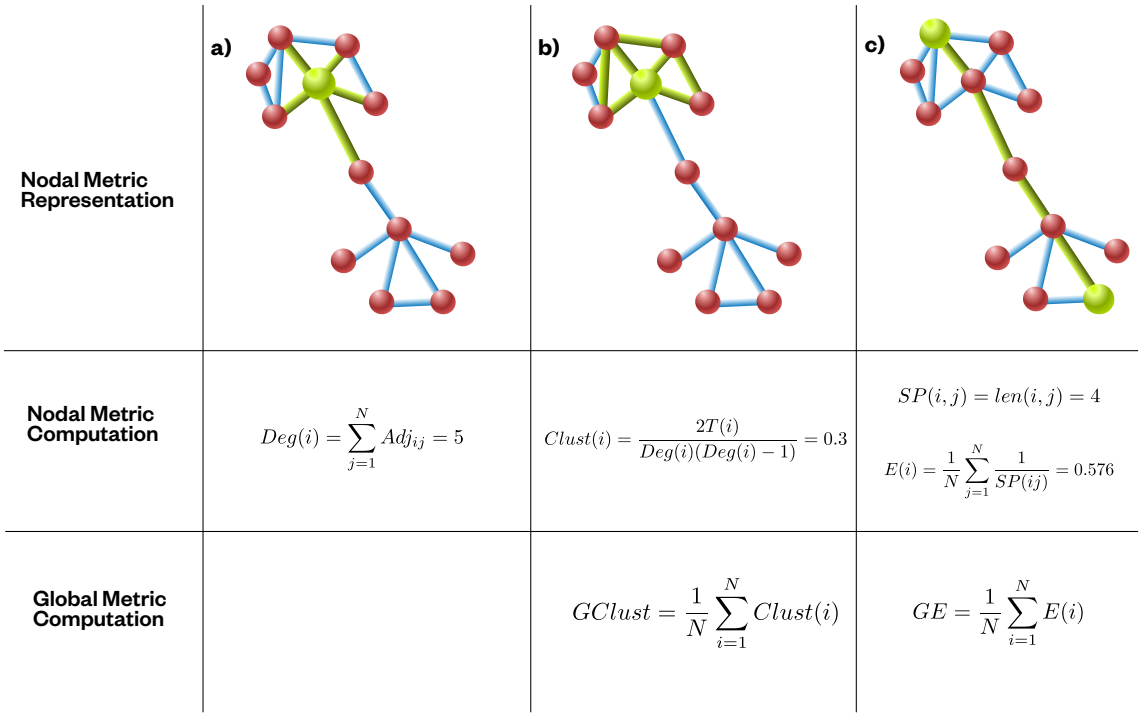


Figure 9: Description and graphical representation of three of the most studied properties of graphs. In a) degree of connectivity (Deg) is represented as the number of connections of a node, in b) clustering coefficient (Clust) as the ratio of triangles in which a node is included related to its degree, and in c) the efficiency (E) based on shortest path length (SP).

3.3. The Brain as a Complex Network

We know since the 19th century that the brain can be defined as a network in that it consists of a set of interconnected elements (neurons)[108]. Furthermore, it is considered a complex network, which are networks whose topological structure is not purely regular, not purely random [123]. We can find various systems organized as complex networks, like social networks, the World Wide Web, biological networks, or electrical networks. One interesting thing about complex networks is that they all share features like a heavy-tailed degree distribution, a high clustering coefficient, and a hierarchical structure [124]. It is interesting to note that these properties just emerge as the network develops, but they will determine how the communication is performed and, thus, the network's function.

3.3.1. Small-Worldness and the Brain

Specifically, the brain pertains to a category of complex networks called "small-world" networks [125]. Small-world networks are characterized by having a few connections over the possible amount (about 10%), a high clustering coefficient, and a short path length (or high efficiency since it is inverse to the path length). All of these features produce a network with highly specialized subnetworks (a group of very highly connected nodes) and easy communication between them (because of the short path length). Also, the distribution of the degree of connectivity is a heavy-tailed one, which means that

there are many nodes with a few connections and a few nodes with a huge amount of them, which act as information hubs [126].

The small-worldness of the nervous system has been observed at multiple levels. At the microscopic level, White and colleagues studied the nervous system of a *Caenorhabditis elegans*, constructing a graph with its 302 neurons and 5600 connections, observing that the network presented all the features of small-worldness [127]. This same structure has also been found on cultured neurons, showing the emergence of small-worldness from isolated neurons [128]. At a macroscopic level, multiple types of brain networks can be constructed depending on how we define the edges (interactions). The properties of structural connectivity networks have been studied using Diffusion Tensor Imaging, an MRI modality that infers WM tracts by the direction of water movement. Dividing the brain at different resolutions (from 70 regions to hundreds), all the structural connectivity networks that have been studied also showed small-world properties, which points to a fractal structure of the networks [129–131]. Finally, FC networks are probably the ones that have received more attention, especially with the refinement of analysis techniques for r-fMRI data. Multiple metrics have been used to define FC, and a lot of different resolutions have also been used for constructing the networks, but regardless of the strategy for building the graph, the small-world topology was always maintained [132–135].

3.3.2. Integration and Segregation

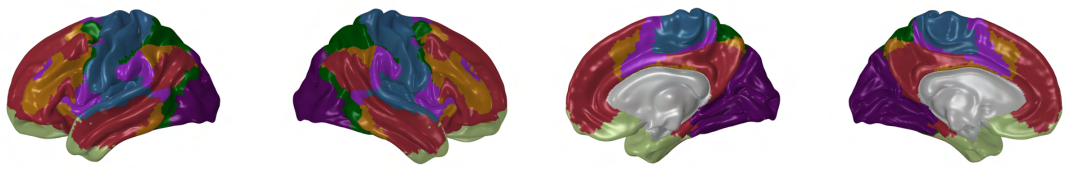
The small-world organization produces various modules that are highly specialized, which means that their nodes are greatly integrated between them but highly segregated from the nodes of other modules. However, despite strong evidence supporting this organizational structure of the brain, why and how it is developed remains unknown. A strong hypothesis relates small-worldness to the concept of "economy" in network analysis, a term that refers to the cost-benefit balance. Thus, this hypothesis states that the brain network is created by a compromise between minimizing biological cost and maximizing integration [136]. Considering that even a brain functional network is embedded in physical space and that multiple synapses (which cover more physical distance) are more metabolically costly than one, physical distance has been proposed as "wiring cost" [137]. According to this, the small-world brain organization is economical as it consists of densely connected proximate areas with a few connections with distant regions, and these properties have been reproduced by economical network models [138].

In order to be economical, two critical concepts in the development of the small-world functional organization of the brain are integration and segregation. Integration refers to the process by which the FC between different parts of the brain increases, and segregation is quite the opposite, a decrease in FC. These two processes form the different functional networks and occur during neurodevelopment, as will be further explained in Section 4.1. Briefly, in the earliest stages of development short-range connections are established, so each part of the brain is functionally connected to anatomically proximate

regions. However, with synaptic pruning some of these connections disappear, and when long-range connections become economically viable due to structural maturation of the brain, there is a segregation between some close regions and integration between distant ones [139].

3.3.3. Brain Functional Networks

This process of simultaneous integration and segregation gives rise to the functional organization of the brain, which is composed of a modularized efficient structure (small-world). The modules of this network are highly specialized structures that serve different purposes in its functioning, being also related to different cognitive domains. They are also called FNs, a concept introduced in Section 2.3 as groups of regions with similar temporal patterns and, thus, high FC [140]. There are multiple functional parcellations of the brain depending on the nodes and how we define relational metrics, but as an example, we will break down one of the most widely used ones that divides the brain into seven functional networks (Figure 10)[19]. This parcellation is the one that will be used in this work to interpret the results obtained from statistical analysis.



Visual Network (VN): It comprises the occipital cortex and is related to the reception and integration of visual information (although other brain regions are involved in visual perception as an experience).

Sensorimotor Network (SN): It contains the postcentral and precentral gyri as well as the supplementary motor area and it is engaged when motor activity is required or for receiving sensory information from the body.

Dorsal Attentional Network (DAN): Comprises distributed regions mostly in the dorsal part of the brain and it is related to top-down attention.

Ventral Attention Network (VAN): It is conformed to multiple brain regions and it is associated with bottom-up attention or salience.

Limbic Network: Located in the rostromedial part of the brain, this FN is related to emotion.

Frontoparietal Network (FPN): Several distributed regions related to executive functions.

Default-Mode Network (DMN): It is composed of multiple widespread regions and it is related to the "inner" mental activity, like mind wandering or episodic memory.

Figure 10: Parcellation of the human brain in the seven functional networks described in Thomas Yeo *et al.* [19]. There is also a brief description of each functional network and the cognitive functions it is related to.

It is important to note that the different FNs are not independent systems but form a whole brain network, and they may have even different functions in it. For instance, the

regions of the DMN are known to have the greatest degree of connectivity of the whole brain, serving as hubs of information [126]. Another example of the interdependence between different FNs is their relationship in the case of DMN and FPN, which show opposite activity patterns (this issue will be further explained in Section 4.3) [141]. Furthermore, the cognitive functions associated with the different FNs are typically related in the same way. For example, in the case of the FPN and the DMN, one cannot simultaneously be engaged in a goal-directed action and mind wandering. And so, a systems science perspective of the brain forces us to consider the mind in the same manner, as a set of interrelated functions instead of purely segregated cognitive processes.

4. Neurobiological Models of ADHD

With recent advances in medical imaging techniques such as Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) we have been able to characterize brain structure and function. Moreover, it has helped us understand how the brain is related to the mind and to different cognitive functions, thus trying to obtain differential patterns in brain disease. In the case of ADHD, these differential patterns have been used to elaborate neurobiological models that explain its etiology and symptomatology, with the ultimate goal of obtaining reliable biomarkers that allow an objective diagnosis of the disease. Here I will summarize the main neurobiological models of ADHD.

4.1. Maturational Lag Hypothesis

This model comes from the diagnostic criteria of ADHD, which states that the disease is defined by a delay in maturation instead of an aberrant brain configuration [10, 142]. The first time this hypothesis was proposed was in 1973 when Marcel Kinsbourne posited that the Minimal Brain Dysfunction (a category that included ADHD by then) was characterized by immature brain processes or primitive (in an ontogenetic way) cognitive strategies [143]. At that time, the model was based purely on symptomatology, but later neurobiological findings observed brain characteristics in ADHD patients that resembled those of subjects of younger ages, thus partially supporting the conception of ADHD as a maturational delay [10, 142, 144].

Brain development is a long process that starts in the third gestational week and elapses until 25-30 years if not the whole lifespan (brain properties are still changing until death, but whether these changes are development or not is under debate)[145]. Both genetic expression and environmental events contribute to brain maturity, transforming the organ from an inefficient structure to an efficient one. Neurodevelopment is a very complex process, but all the characteristics are related to making the brain network more efficient, which is summarized by fast transmission of information and low metabolic cost. For this aim, it is necessary to develop many connections between neurons and then keep only the necessary ones. So there is first a vast increase in synaptic connections and then a process called synaptic pruning, which consists of eliminating redundant or unnecessary synapses. This process is especially important in the cerebral cortex, or GM, which is the brain's outer layer. Another process that occurs during adolescence in GM is the reduction of its thickness, which implies an inverted-U shape of cortical thickness trajectory, increasing during childhood and then decreasing again [146].

That works well for spatially close neurons, but there is still the problem of long-range connections, like the inter-hemispheric ones. Of course, the fastest way to cross the brain from the right to the left extremes is through the center, but it is still a long distance. To increase the speed of information transmission between these areas, there is a substance called myelin that covers the axon of the neuron allowing efficient transmission

of information between distant areas [147]. This process is known as myelination and occurs primarily in the neurons of the inner part of the brain [147, 148].

These two processes also impact the functional organization of the brain. At first, FC is higher between spatially proximate areas, that is, neurons tend to coactivate with those around them. However, as age increases, they start forming distant connections and constitute the FN [139]. So FC maturation is described by the segregation (decrease of functional connectivity) of spatially close regions and the integration (increase in functional connectivity) between distant regions in an organized manner. Another remarkable fact that comes with functional specialization is the development of negatively connected regions, which are regions that have opposite activity patterns (when one of them increases activity, the other one decreases activity) like the DMN and the FPN, which will be of special relevance in the DMN interference hypothesis.

Evidence supporting the maturational lag hypothesis has been found in multiple brain properties, from electrical activity to the shape of some structures or the brain's functional organization. The first neurobiological signs of the hypothesis were found in altered electric activity using Electroencephalogram (EEG) [149] and delayed myelination [150]. After that, various studies reported delayed trajectories in GM development, that is, the peak cortical volume was reached later in youth with ADHD than in healthy controls, and so did the reduction in that metric [144, 151–153]. But the delayed development was not reduced to brain morphology, and signs of immaturity were also found in functional organization, specifically in reduced segregation between different brain networks [154]. There is also a debate on whether these immaturity signs normalize with age, mostly based on the reduction of prevalence of ADHD in adulthood (as seen in Section 1.2). By now, opposite information has been found on this matter, with some studies finding a meeting point between the two trajectories (healthy people and people with ADHD)[144, 153] and other studies that suggest that the signs of immaturity remain [21, 155–157]. Altogether, these seemingly contradictory results can be due to two subtypes of ADHD, one that never normalizes and another one that remits.

4.2. Dual-pathway Model

As seen in Section 1.5.1, the Dual-Pathway model was proposed based on ADHD neuropsychology and its subtypes, positing that the inattentive symptoms were due to deficits in a "cool" processing stream while hyperactivity/impulsivity were related to an alteration of a "hot" one [11, 12]. Moreover, the description of the corticostriatal circuitry provided neurobiological support for this hypothesis [158]. The subcortical structures receive and send information to cortical regions engaged in three different functions: some are related to emotions, others are engaged in associative or executive functions, and others take part in sensorimotor functions. Thus, subcortical structures receive sensory information about an environmental situation, then communicate with limbic (emotional) regions to evaluate and estimate the rewards corresponding to each possible action. Then, the representation

of the reward is sent to associative/executive cortices for planning the actions necessary to get it. Finally, with the input of this plan, the subcortical structures can send proper instructions to the motor cortices to engage action [158]. So according to this model, there are different pathways for the "cool" functions (the corticostriatal circuits involving associative cortices) and for the "hot" ones (the circuits involving limbic regions).

Furthermore, this model has found support in neuroimaging studies in the form of volumetric alterations in areas related to these circuits, including the basal ganglia [159, 160]. Task-based fMRI studies have also found abnormal activity that is independent between both systems, supporting the model as well [161, 162]. Even with functional connectivity, results coherent with this hypothesis have been found, showing that reduced functional connectivity in the hot pathway is related to emotional lability and reduced functional connectivity within the cool pathway correlates with executive deficits [63]. Also, employing short-range and long-range functional connectivity, Tomasi and Volkow [163] found simultaneous alterations in areas related to the reward-motivation system and areas related to attentional deficits, suggesting that the first were related to motivation and the latter to executive deficits [163].

4.3. Default Mode Network Interference Hypothesis

If the latter model was based on the distinction of two independent streams of the brain for explaining ADHD symptomatology, the DMN interference hypothesis focuses on the relation between two FN of the brain as the main neurobiological property underlying ADHD. This model is substantiated in resting-state fMRI data, specifically in the FC between two functional networks: the DMN and the FPN.

The DMN is one of the most robustly described brain FN. It was reported for the first time using PET, including several regions in which metabolic activity was reduced during mental tasks [164]. That led to the conclusion of specific brain regions as related to a "default-mode" of the mind, that is, internally focused wandering, autobiographical memory... and if these regions' activity becomes increased during these inner tasks, it also decreases when the mind is focused on outer stimuli like problem solving. The DMN comprises two main components that converge on a core composed of two regions: the Posterior Cingulate Cortex (PCC) and the medial Prefrontal Cortex (mPFC). The remaining subsystems are the Dorsomedial Prefrontal Cortex (DMPFC), which is engaged in recognizing our own present mental state as well as other people's (which is called Theory Of Mind), and the Middle Temporal Lobe (MTL) subsystem, more engaged in both future and past scene construction [165].

If the DMN is the main functional network of "inner" mental activity, the FPN or executive network is quite the opposite, engaged for goal-directed tasks (a.k.a. cognitive control). This network is the brain correlated with executive functions of the mind (Described in Appendix 2), so it manages processes like working memory, response inhibition, decision making, or sustained attention [166]. As its name suggests, the FPN

comprises a variety of distributed regions mainly in frontal and parietal areas, and their primary mission in the whole-brain network is to join and process information from different brain systems [23].

The DMN and the FPN present, thus, opposite patterns of activity, which means that when one's activity increases, the other one's decreases. Furthermore, the strength of this negative relationship is related to behavior, specifically to response inhibition as measured by the flanker task response time [22]. The DMN interference hypothesis posits that this functional network (the DMN) is not appropriately suppressed during goal-directed tasks, creating an interference [13] that could be cognitively translated into inner thoughts intruding during task-related mental activity. Various studies have found evidence supporting this model in both DMN overactivity during goal-directed tasks and decreased negative connectivity between the DMN and the FPN at rest [167–169].

4.4. Multi-network Models

Multi-network models use the interaction between multiple brain systems to explain ADHD's etiology [170]. Under this definition, the DMN interference hypothesis is an example of a multi-network model, but it proved insufficient when other functional brain networks were analyzed. The most straightforward case is the one of the Ventral Attentional Network (VAN), which is related to bottom-up attention or salience [171]. Its role in the interplay between the DMN and the FPN is easily explainable by the cognitive sequence of the salience process. If a subject is wandering, that is, focused on his inner thoughts and there is a very salient stimulus (e.g., strident noise), the focus of the thoughts suddenly changes from inwards to the outer world, trying to understand what is the cause of the stimulus. So in terms of brain function, when there is a salient stimulus, the VAN disengages the DMN and engages the FPN [171–173]. Now it is easy to see that a malfunction of the VAN could result in inefficient deactivation of the DMN, which would lead to the DMN interference hypothesis. Furthermore, numerous studies point to VAN-DMN abnormal interaction in ADHD [14, 21, 154].

The incorporation of the VAN to the DMN interference hypothesis just puts in relevance how interrelated the functional systems are and how difficult it is to limit the alterations to a few of them. As it happened in the case of neuropsychology, functional networks are constructs that define some part of the brain based on a criterion, so they are truly related and the burden between them is not as categorical as it may seem. Considering this interrelation in both the mental and the neurobiological planes, it is important to take into account all brain systems when studying a psychiatric condition [174]. Actually, in ADHD, alterations have been found in all Yeo-Krienen functional networks [19]: from basic sensorimotor [175–178] to higher order cognitive circuits like the ones described before [170].

MOTIVATION AND AIMS

Motivation

As shown in the introduction of this dissertation, ADHD is an important public health issue affecting millions of people's quality of life. Our understanding of the disorder is continually evolving, changing the way in which it is diagnosed and treated [179]. However, many questions remain unanswered in terms of the disease characterization and its relation with age, like how immature must behavior be to be considered ADHD and if adult and child forms of the disease present different characteristics. Also, the high remission rate of children when reaching adulthood raises the question of whether there is indeed a true remission with age or if the mental and neurobiological "stability" of maturity allows people with slower maturation rates to catch up. If this were the case, we would be facing a big problem of overdiagnosis, with severe consequences such as the intake of psychostimulants like amphetamines during their development without any need. For all these reasons, it is crucial to better understand the neurobiology of ADHD with the final aim of obtaining reliable, objective biomarkers that allow us to diagnose the disease accurately.

To get these biomarkers, we have to develop a good model that describes the brain of people with ADHD in a precise way. Several models have been proposed during the past three decades, the first ones were based on structural and task-related activity abnormalities and involved a few regions, while later models progressively included more and more brain areas and the interactions between them. However, based on the evidence supporting them, not even the most reductionist ones have to be necessarily wrong but somewhat incomplete descriptions of a broader alteration of the brain network structure. Because of this, this dissertation will try to use methods that aim to describe the brain of people with ADHD in a way that encompasses the previous models and, hopefully, shed some light on understanding the disease.

The first method is called Stepwise Functional Connectivity (SFC) [23] and is based on the social science experiments of Milgram [180, 181] that led to the concept of the "six degrees of separation" between two points in a small-world network. This method explores the hierarchical topology of a network in terms of how the information is successively integrated first in provincial hubs (hubs of a network module) until the global hubs of the network. The method's technical details are described in *Study 1*, but briefly, it computes the number of connections between the primary sensory cortices and each voxel at different functional distances (path length). In that way, we can explore the integration of the sensory cortices at direct functional distance, the integration of information in multimodal association cortices at medium functional distance, and the cortical hubs at long

functional distance. These different properties of the functional network can be related to its functional maturation and provide information about the integration and segregation of different FNs.

The second method is called Local and Distant Functional Connectivity (LFC/DFC)[182]. It measures the degree of connectivity of each voxel within its neighborhood (a 28 mm^3 cube whose center is the voxel) and with the voxels outside this neighborhood. Again, the technical details are explained in both *Study 2* and *Study 3*. This method is related to neurodevelopment due to the local-to-distant connectivity maturation pattern of some brain areas [139]. In the case of local connectivity, the metric can reflect altered integration if it affects an area of one FN or altered segregation if it lies in the boundary separating various networks.

Altogether, the usage of these two methods will provide information about some properties of the whole brain network that has not been studied in ADHD. We hypothesize that the results obtained can be explained under the current neurobiological models of ADHD, thus suggesting that they are all different aspects of the same phenomenon.

Aims

The present dissertation aims to determine whether there is an alteration of the global brain organization in people with ADHD that may underlie the features that characterize the different neurobiological models of the disorder. For that, we will apply two different graph-theory methods based on systems science to the resting-state functional Magnetic Resonance Imaging data of adults and children with ADHD. Both of these methods study spatial properties of the brain functional network, but while Stepwise Functional Connectivity [23] focuses on topological space proximity, Local and Distant Functional Connectivity [182] is more related to the relation between the topological and the physical ("real-world" euclidean) spaces. The prelude to this work was a study that compared the SFC patterns between children with ADHD and neurotypically developing children (ND), which will be discussed in the last section of the dissertation [178]. The following studies extend that work in various terms, the first one is an application of the same method to adults with ADHD, while the second and the third one apply Local and Distant Functional Connectivity analysis to the same sample of children and adults respectively, to see if the information flow in topological and physical spaces are related. So the three studies that compose this dissertation are organized as follows:

Study 1

Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder.

Aim: To explore the integration of information from sensory to associative cortices in medication-naïve adults with ADHD. These processing streams will reflect the topological architecture of the whole brain network, and while it has been studied in children with ADHD, it remains unknown in adults.

Study 2

Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder.

Aim: To study the LFC and DFC patterns in children with ADHD. This graph-theory based method seems suitable for simultaneously evaluating the maturational delay hypothesis and multinetwork models in ADHD regarding segregation between spatially proximate regions.

Study 3

Local Functional Connectivity as a Parsimonious Explanation of the Main Frameworks for ADHD in Medication-Naïve Adults.

Aim: To characterize the LFC and DFC patterns in medication-naïve adults with ADHD. Once these brain properties have been explored in children with ADHD, this study will evaluate whether their patterns are similar in adults or not.

STUDY 1

Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder

Pretus, C., Marcos-Vidal, L., Martínez-García, M., Picado, M., Ramos-Quiroga, J. A., Richarte, V., Castellanos, F. X., Sepulcre, J., Desco, M., Vilarroya, Ó., & Carmona, S.

Human Brain Mapping (2019)

Abstract

Neuroimaging studies indicate that children with attention-deficit/hyperactivity disorder (ADHD) present alterations in several functional networks of the sensation-to-cognition spectrum. These alterations include functional overconnectivity within sensory regions and underconnectivity between sensory regions and neural hubs supporting higher order cognitive functions. Today, it is unknown whether this same pattern of alterations persists in adult patients with ADHD who had never been medicated for their condition. The aim of the present study was to assess whether medication-naïve adults with ADHD presented alterations in functional networks of the sensation-to-cognition spectrum. Thirty-one medication-naïve adults with ADHD and twenty-two healthy adults underwent resting-state functional magnetic resonance imaging (r-fMRI). Stepwise functional connectivity (SFC) was used to characterize the pattern of functional connectivity between sensory seed regions and the rest of the brain at direct, short, intermediate, and long functional connectivity distances, thus covering the continuum from the sensory input to the neural hubs supporting higher order cognitive functions. As compared to controls, adults with ADHD presented increased SFC degree within primary sensory regions and decreased SFC degree between sensory seeds and higher order integration nodes. In addition, they exhibited decreased connectivity degree between sensory seeds and regions of the default-mode network. Consistently, the higher the score in clinical severity scales the lower connectivity degree between seed regions and the default mode network.

1. Introduction

Attention-deficit/hyperactivitydisorder (ADHD) is a neurodevelopmental disorder characterized by excessive levels of inattention,impulsivity,and hyperactivity [25]. Approximately35% of children with ADHD still fulfill DSM-IV diagnostic criteria for ADHD in adult life [183].

Neuroimaging research on ADHD has typically focused on net-works supporting higher order functions, with little attention to findings in primary sensory regions. For instance, several studies report a weaker segregation between cognitive control networks and default mode network both in children and adults with ADHD [167, 168, 184–186], although only a few studies highlight the need to clarify how sensory regions interact with higher order association networks in ADHD [187, 188]. In response to this, recently developed analysis tools such as the step-wise functional connectivity (SFC) approach [23] allow evaluating the presence of abnormalities in multilevel information processing systems from early sensory to higher order cognitive circuits in the brain.

Making use of an SFC protocol, Carmona *et al.* [178] provided evidence that the information flow between primary sensory cortices and higher order association nodes might be disrupted in children with ADHD. Compared with controls, children with ADHD presented increased interconnectivity within primary sensory cortices at initial steps of the sensation to-cognition-continuum [178]. At the final steps of the sensation to cognition continuum, children presented decreased SFC degree with executive processing areas and increased SFC degree with DMN areas. These studies indicate atypical connectivity transitions between sensory and higher order large-scale functional networks, thus potentially compromising the flow of information across the sensation-to-cognition continuum. However, whether this pattern is also present in the adult form of the disorder is still unknown.

The aim of the present study was to test whether medication-naïve adult patients with ADHD show impaired connectivity between primary sensory and higher order cognitive circuits. For this purpose, we applied a SFC protocol aimed to detect which parts of the brain are connected with primary sensory regions not only through direct paths (i.e., one-step functional distance, which would be the standard functional connectivity analysis), but also through indirect connections that involve a varying number of "link-step" distances or "relay stations". Hence, in contrast to other standard methods such as functional connectivity strength evaluation, SFC allows measuring functional connectivity between any pair of brain locations that are connected by any finite number of relay stations.

Based on the assumption that adult ADHD may share similarities with childhood ADHD in terms of functional connectivity alterations, we predicted that our sample of medication-naïve adults with ADHD would show increased SFC within sensory regions, as well as decreased connectivity between sensory seeds and networks supporting executive functions, and increased connectivity between sensory seeds and key nodes of the DMN.

2. Methods

2.1. Participants

A total of 31 adults with combined ADHD and 22 healthy controls were recruited (see demographics in Table 1). We ensured both sexes were well represented in both groups (12 women in the ADHD group and 16 women in the HC group). The ADHD patients were selected by a specialized team of psychiatrists and psychologists from Vall d'Hebron Hospital in Barcelona (Spain), where they were evaluated. All patients met DSM-V criteria [25] for ADHD combined subtype and were medication naïve.

Standard ADHD scales were administered to both groups, including the Conners Adult ADHD Rating Scale (CAARS) [189], the Wender Utah Rating Scale (WURS) [190], and the ADHD Rating Scale [191]. All ADHD scores were significantly higher in the ADHD sample (see demographic data in Table 1).

Characteristic	ADHD (N = 31) Mean (sd)	Controls (N = 22) Mean (sd)	Stat (df)	p value
Age (range 19 to 52)	35.4 (9.9)	30.4 (5.8)	$t(51) = -2.11$	.040
ADHD Rating Scale	32.3 (9.8)	6.0 (5.8)	$t(48) = -11.89$	<.001
Sex (number of women)	16	12	χ^2 (1) =0 .044	n.s.
Number scanned with replacement headcoil	14	6	χ^2 (1) = 1.75	n.s.
Framewise Displacement	.054 (.036)	.036 (.030)	$t(51)=-1.92$	.061

Table 1: Three controls did not complete the attention-deficit/hyperactivity disorder (ADHD) rating scale. Independent sample t-tests or chi-square were used to compare groups.

Exclusion criteria included comorbidity with other psychiatric diseases or personality disorders, assessed by the structured Clinical Interview for Axis I (SCID-I) [192] and Axis II disorders [193]. Participants with substance abuse disorder, including those who consumed tobacco and cannabis within the last 6 months, were also excluded. Participants with an estimated WAIS-III IQ [194] lower than 80 were excluded. The study was approved by the Hospital de Vall d'Hebron Ethics Committee, and informed consent was obtained from all participants before taking part in the study.

2.2. fMRI Image Acquisition and Preprocessing

Images were acquired using a Philips Achieva 3T scanner. T1-weighted images were obtained using a FSPGR sequence (TR: 8.2 ms, TE: 3.7 ms, FA: 88, voxel size: 0.94×0.94, slice thickness: 1.00 mm, gap: 0 mm, matrix size: 256×256×180). An EPI-T2* sequence was used to obtain the resting-state functional volumes in a single run that lasted 5.8 min (116 time points, TR: 3000 ms, TE: 35 ms, FA: 90, in-plane voxel size: 1.80×1.80 mm, slice thickness: 3.0 mm, gap: 1.0 mm, matrix size: 128×128). Due to a technical problem, 11 participants (evenly distributed between groups; χ^2=1.753; p=.186) were scanned using a different radiofrequency head coil (16 channels instead of 8 channels), which was

considered in the analyses. Participants were instructed to remain still and awake with their eyes open during the functional run.

Functional MRI data were preprocessed with the software packages SPM12 (Welcome Department of Imaging Neuroscience, London, UK) and AFNI (Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, MD). After removing the first three volumes, functional images were realigned to the mean image to correct for motion-related artifacts, despiked with 3dDespike AFNI tool (c1=2.5, c2=4), normalized to MNI standard space, and spatially smoothed with a 6 mm full-width-at-half-maximum Gaussian kernel. All functional images were downsampled to 4 mm^3 voxels to facilitate computational calculations [23]. Finally, nuisance covariates (six rigid body realignment parameters, mean white matter, mean cerebrospinal fluid, and mean whole brain intensity signals) were regressed out to minimize the effects of movement.

Given the impact of in-scanner motion on functional connectivity analyses [195–197], participants with a mean framewise displacement (FD) over 0.2 mm as measured by the MCFLIRT tool [198] were discarded. Additionally, we plotted a resting state functional connectivity quality control index (RSFC-QC)[199] to assess the effect of motion in functional connectivity as a function of node distance. The data quality control showed no relationship between functional connectivity estimates and node distance, thus pointing to a reduced effect of head motion artifacts in our data (Supplementary Figure 1).

2.3. SFC Analysis

The SFC analysis allows computing the number of functional paths between previously defined seed regions and every other voxel in the brain at successive numbers of relay stations or "link-step" distances. Intermediate voxels work as relay stations or "link-steps" that range between 0 (direct, one link-step connection) and 6 (seven link-step connections) before stabilizing [23] (see Figure 12). Based on the number of relay stations, the degree of functional connectivity can be classified as direct (one link-step, and thus zero relay stations), short (two and three link-steps), medium (four and five link-steps), and long (six and seven link-steps).

For each processed brain, we computed the whole-brain connectivity matrix by calculating the Pearson's correlation coefficient r for each pair of voxels. From this point onwards, only positive correlations were considered given the challenge of interpreting negative correlations after global signal regression in functional connectivity studies [200, 201]. Correlation matrices were then filtered to contain only correlations surviving false discovery rate (FDR) correction (q<0.001). The resulting matrix was then binarized. As a result, we obtained an unweighted "one link-step" matrix for each subject containing ones for each pair of voxels whose signals were significantly correlated and zeros otherwise.

In parallel, a set of three masks including three bilateral sensory seed regions was designed, each encompassing eight voxels (each voxel was 4 mm isotropic) forming a

cube. Following Sepulcre *et al.* [23], the MNI coordinates for the most anterior, lateral, and superior voxel of each cube was [8,−76,10] in the primary visual cortex, [56,−12,10] in the auditory cortex, and [0,−28,66] in the somatosensory cortex. To assess the degree of combined SFC of all sensory seeds irrespective of modality, a fourth mask was built combining information from all three primary sensory regions.

Each n-step map encoded the number of n-step connections (SFC values) between every voxel in the brain and the voxels within the mask including the three bilateral seed regions. At each link step, SFC maps were standardized to Z-scores by subtracting the mean and dividing by its standard deviation to yield SFC values. Henceforth, we refer to these Z-score values as the SFC values. A more detailed description of the SFC method can be found in Sepulcre *et al.* [23] and Sepulcre [24].

2.4. Statistical Analysis

All the statistical analyses were performed using SPM12. Groups were homogeneous for mean FD, head coil, sex, and IQ but differed in age (t=−2.11; p=.04).

For each of the seven SFC maps, general linear models were fit for each group separately. These models included age (mean centered to zero), FD (mean centered to zero), and head coil as covariates of no interest. Statistical inference was performed over the intercept of the models to identify SFC values significantly greater than zero. Since this analysis was performed for exploratory purposes only, we displayed clusters of at least 10 contiguous voxels surviving an uncorrected p<.01.

General linear models were also fit to compare the seven SFC maps between groups. These models included group as a variable of interest and age, sex, FD, and head coil as variables of no interest (age and FD were mean centered to zero). Even though FD, sex, and head coil did not differ significantly between groups, they were included as a precaution. For each model, we tested the effect of group through a t-test on the value of its estimate.

In addition to group differences, we tested the association between symptom severity —ADHD Rating Scale— and functional connectivity profiles in each step within the group of ADHD patients. In this correlation analysis, we included head coil, FD, sex, and age as nuisance covariates.

As supplementary analyses, we explored if group differences were consistent across gender (see Supplementary Figure 3) and across the three main sensory modalities (see Supplementary Figure 4). In addition, we measured the predictive power of the group differences using the software PRoNTo [202] (see Figure 5 and Table 1 in Supplementary Material).

To correct for multiple comparisons, we used a Monte-Carlo simulation implemented in the AFNI 3dClustSim function [203] (accessed July 18, 2018). This method was used to obtain an experiment Family Wise Error (FWE) corrected type 1 error probability of

0.05 (α^{FWE}=.05). To achieve it, we needed a map FWE corrected type 1 error probability of .0071 (because we have 7 maps and 0.05/7=0.0071). For this purpose, we thresholded the statistical maps with a minimum cluster size of 174 contiguous 4 mm^3 voxels surviving the uncorrected p<.05.

2.5. Cortical Network Visualization

To facilitate interpretation of results in the context of large-scale functional networks, the percentage of significant voxels that overlapped with each of the seven cortical resting-state functional networks described by Thomas Yeo *et al.* [19] was calculated for each analysis using MATLAB 2019a.

Surface projections of SFC maps were performed via a Matlab in-house script that uses nearest neighbor (for Yeo's atlas) or linear (for the quantitative maps) interpolation and the surface normals to project cortical voxels onto the surface. The surfaces employed were the left and right "Q1−Q6_R440.#.midthickness.164k_fs_LR.surf.gii" of the software Connectome Workbench [204]. To avoid redundancy, we only present stepwise connectivity profiles of the left hemisphere with uneven step numbers in the main document.

3. Results

3.1. SFC maps in patients with ADHD and healthy controls

The combined SFC maps for adult patients with ADHD and healthy controls are shown in Figure 11, respectively. As expected, at short linkstep distances (one and three link-step maps), both groups exhibited functional connectivity between the sensory seeds and primary sensory regions. At longer link-step distances (five and seven link-step maps), functional connectivity between sensory seed regions and frontoparietal areas was established in both groups. In turn, healthy controls showed connectivity with medial frontal areas and the precuneus at longer link step distances, which was not observed in the ADHD group.

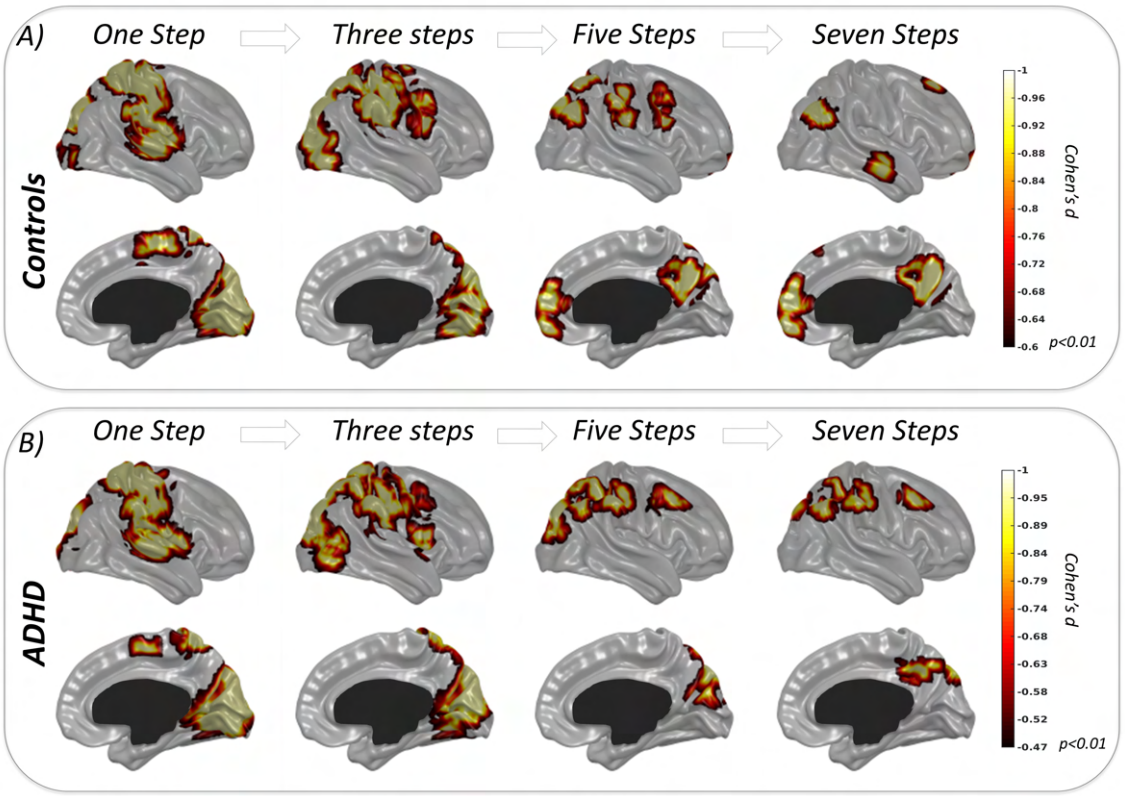


Figure 11: Surface projections of the one-sample t-test results of uneven link-step distances for (a) the adult sample of ADHD patients and (b) the control sample of healthy adults. Each image represents Cohen's *D* ranging from the value that corresponds with a $p<.01$ (.6 for the control sample and .47 for the ADHD sample) and a value of 1. Cohen's *D* effect sizes greater than 1 are collapsed to 1. Left hemispheres are displayed. Abbreviation: ADHD, attention-deficit/hyperactivity disorder

3.2. Between-group Differences

Between group comparisons are shown in Table 2 and map projections of between-group differences are presented in Figure 12. All results were corrected for multiple compar-

Between-subject Comparison	Peak MNI Coordinates			No. of Voxels	Highest *t* score	Cluster-level *p* value
	x	y	z			
One-step						
Three-steps						
ADHD >Controls						
L calcarine	-4	-64	16	248	3.25	<.001
Five-steps						
Controls >ADHD						
L medial orbitofrontal gyrus	-4	58	-17	185	3.62	.001
ADHD >Controls						
L calcarine	-4	-68	16	398	3.47	<.001
Seven-steps						
ADHD >Controls						
R lingual gyrus	16	-61	-9	283	3.17	<.001

Table 2: Results of the stepwise functional connectivity (SFC) analyses, including between-group comparisons (adults with attention-deficit/hyperactivity disorder [ADHD] vs. healthy controls) for each SFC map at different functional distances (one-step to seven-steps). Results were corrected for multiple comparisons by means of a Monte-Carlo simulation.

isons (see Section 2.4 of this study). The analysis revealed functional connectivity differences starting from the three-step connectivity maps, with ADHD patients exhibiting increased seed region connectivity with the left calcarine sulcus compared to controls. These functional connectivity differences were maintained until the seven link-step maps, which exhibited between-group differences that peaked in the right lingual gyrus.

Patients with ADHD showed decreased functional connectivity in the five link-step distance map in the left medial orbitofrontal gyrus compared to controls. These differences, group differences of 55.6, 64.08, and 62.46% for three, five, and seven link-steps distances, respectively (see Figure 5 and Table 1 in Supplementary Material).

3.3. Association with ADHD Symptom Severity

Table 3 and Figure 13 show the results of the regression analysis with the symptom severity scales. As observed in Figure 13, symptom severity was positively associated with the degree of functional connectivity in the left middle frontal gyrus and the right superior temporal gyrus, regions that largely overlapped with the sensory-motor network (56.65% in three link-step, 59.88% in five link-step, and 60.42% in seven link-step maps) and the dorsal attention network (28.24% in three-step, 26.38% in five link-step, and 25.57% in seven link-step maps). With regard to negative correlations, we found that the higher the ADHD rating scale score the lower the degree of functional connectivity in the bilateral superior frontal gyrus, clusters that largely overlapped with the DMN (68.15% in three link-step, 64.14% in five link-step, and 62.96% in seven link-step maps) and the frontoparietal network (21.17% in three link-step, 25.50% in five link-step, and 25.05%in seven link-step maps). The associations between ADHD symptom severity scores and mean SFC values in each significant cluster per link-step distance map are illustrated in

Figure 13.

4. Discussion

The present study aimed to elucidate how primary sensory regions interact with higher order association networks in adult ADHD, a disorder that is typically approached with a strong focus on higher order cognitive functions in neuroimaging research. Hence, we used SFC to assess multi-level information processing between early sensory and higher order cognitive circuits in the brain of medication-naïve adults with ADHD compared to healthy adults. Our results partially align with a previous SFC study on children with ADHD [178], suggesting that the increased functional connectivity within sensory regions may persist in adult hood. However, sensorial integration into the DMN was lower in adults with ADHD compared with controls, the reverse pattern of that found in children with ADHD (hyper-connectivity) [178]. Thus, deviations from typical SFC patterns in adult ADHD only partially resembled those observed in children with ADHD in previous studies. The correlations between SFC values and symptom severity in the adult ADHD sample corroborated the between-groups findings. In particular, ADHD rating scale scores were positively associated with increased functional connectivity within the somatosensory-motor network and between seed regions and the dorsal attention network, and inversely associated with functional connectivity between sensory seed regions and the DMN and the frontoparietal network at short, medium, and long functional distances. We discuss each of these findings below.

4.1. Increased SFC in Visual Cortices

Our results indicate increased functional connectivity between primary sensory areas and the visual cortex in adults with ADHD compared to controls. These findings are in line with Carmona *et al.* [178] observations in children with ADHD, suggesting a similar pattern of deviations in children and adults with ADHD at intermediate and long functional distances. However, while children with ADHD showed hyperconnectivity within a small area of the lateral occipital cortex at short link-step distances, the differences cover almost all of the bilateral medial occipital cortices in adults with ADHD (including V1, V2, V3, which are part of both the dorsal and the ventral visual circuitry), and are present at short, intermediate, and long link-step distances.

We believe that increased connectivity at medium and long functional distances may reflect the general visual network hyperconnectivity frequently described in children with ADHD [16, 135, 175, 177]. Our results suggest that at least part of the sensory information in adults with ADHD keeps reverberating within the visual loops, decreasing the information flow between sensory regions and neural hubs supporting higher order cognitive functions. In addition, our observations support the notion that existent models of ADHD would benefit from incorporating alterations in primary sensory areas, which are often ignored or taken as a false positive [187] but may nonetheless significantly alter multilevel information processing in ADHD.

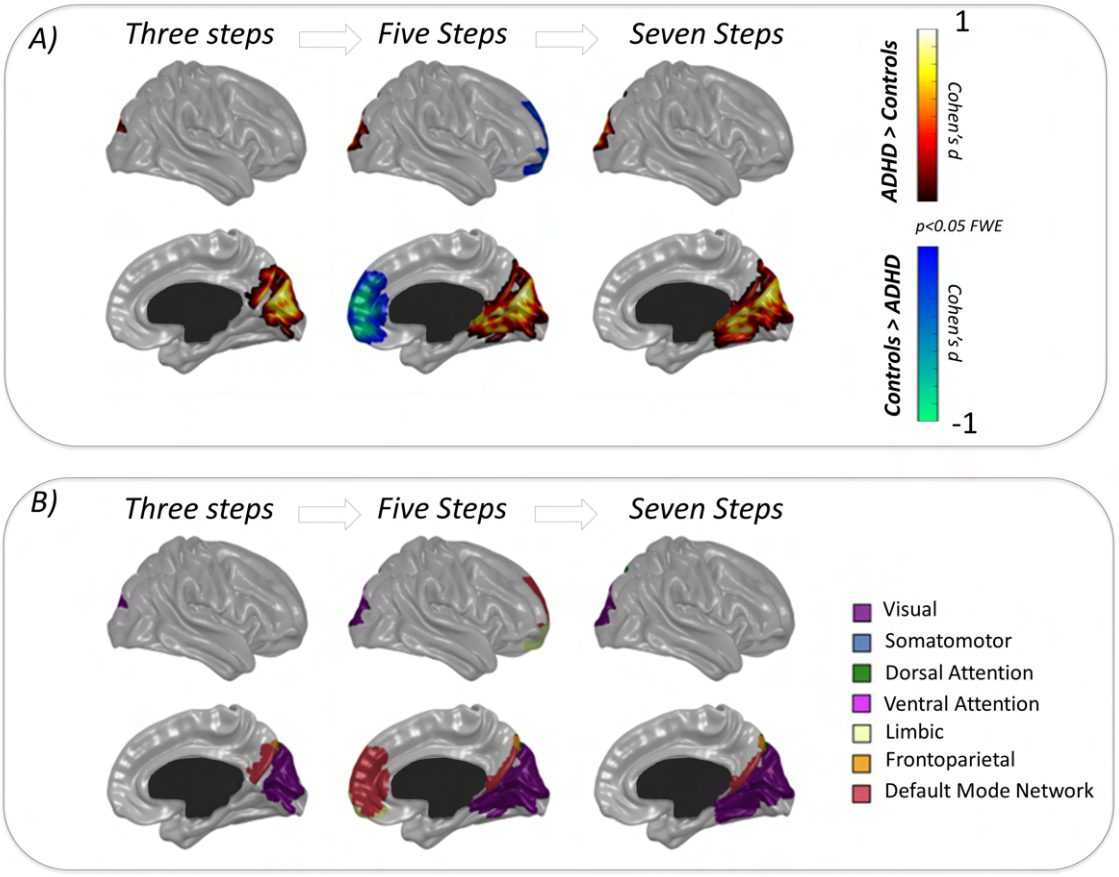


Figure 12: (a) Surface projections of the two-sample t-test results of uneven link-step distances for the between−groups' contrast between adult ADHD patients and the control sample. Images display Cohen's D effect sizes, and the positive (hot) and negative (winter) color maps range from the absolute value corresponding to an uncorrected p<.05 to an absolute value of 1. Values greater than 1 and lower than −1 are collapsed to 1 and −1, respectively. Subplot (b) indicates to which large-scale resting-state functional networks the significant voxels belong according to the parcellation of Thomas Yeo *et al.* [19]. Left hemispheres are displayed. Abbreviation: ADHD, attention-deficit/hyperactivity disorder

4.2. Decreased SFC in DMN Regions

While the intravisual loops were more functionally connected in adults with ADHD compared to controls, the circuits connecting sensory cortices with areas associated with higher order cognitive functions were weaker. At medium functional distance (five link-step distance), adults with ADHD exhibited reduced degree of functional connectivity with, predominantly, the DMN, and with the frontoparietal and limbic networks to a lesser extent. Such differences do not necessarily imply a less direct connection between sensory regions and the DMN. Since our measurements of between-region functional connections included a number of relay stations (which define functional distance), these differences could be due to: (a) a weaker connection between the sensory cortices and the relay stations, or (b) a weaker connection between the relay stations and areas associated with higher order cognitive functions. Since the direct functional connectivity between primary sensory cortices and the relay stations was not weaker, the most likely compromised

loops are those connecting relay stations (attentional or secondary sensory cortices) with the DMN.

These results are in line with studies pointing at deficits in DMN interconnectivity in adult ADHD, for example, decreased functional connectivity between the anterior cingulate cortex and the precuneus/posterior cingulate cortex [167], decreased network homogeneity in the DMN [205], and distributed hypo-connectivity within the DMN [21]. Additionally, children with ADHD have been found to exhibit decreased short and long-range functional connectivity density in regions of the DMN [163] and increased local functional connectivity in the boundaries of the DMN [16]. In adults with ADHD weaker segregation has been found between the DMN and cognitive control networks [186]. Altogether, these results point to a lack of integration in DMN regions and a lack of segregation between DMN and task positive networks.

ADHD Rating Scale	Peak MNI Coordinates			No. of Voxels	Highest r	Cluster-level p value
	x	y	z			
One-step						
Three-steps						
Positive association						
L middle frontal gyrus	-36	3	59	556	0.68	<.001
Negative association						
R superior frontal gyrus	20	31	53	496	0.64	<.001
Five-steps						
Positive association						
R superior temporal gyrus	56	-35	21	1179	0.62	<.001
Negative association						
L superior frontal gyrus	-28	65	15	859	0.71	<.001
R precuneus	12	-58	35	184	0.59	.001
Seven-steps						
Positive association						
R superior temporal gyrus	56	-35	21	1185	0.61	<.001
Negative association						
L middle frontal gyrus	-40	23	46	287	0.70	<.001
R superior frontal gyrus	-28	65	15	441	0.65	<.001
R precuneus	12	-58	35	206	0.61	.001

Table 3: Results of the stepwise functional connectivity (SFC) analyses, including positive and negative associations of the attention-deficit/hyperactivity disorder (ADHD) rating scale in adult ADHD patients with each of the SFC maps at different functional distances (one-step to seven-steps). Results were corrected for multiple comparisons by means of a Monte-Carlo simulation.

As a part of the DMN, the medial prefrontal cortex (mPFC) was particularly affected in our sample. ADHD-associated alterations in the mPFC have been reported in a wide variety of studies, including altered functional connectivity with other DMN nodes [167, 205], reduced deactivation while completing a task [206], and slower cortical thinning in children with higher symptom severity [207]. Since the mPFC plays a key role within the DMN, the sensory hypoconnectivity with the mPFC observed in the present data set could be pointing at alterations in DMN-associated functions such as mind-wandering

[208], which could underlie attentional deficits in ADHD.

Our findings contrast with those in Carmona *et al.* [178], which found greater SFC in the DMN in children with ADHD. In general, the DMN undergoes intense maturational changes with age as it transitions from sparse within-network functional connectivity in typically developing children to a more robustly interconnected network in neurotypical adults [209]. On a speculative note, the hypoconnectivity and hyperconnectivity profiles observed at long functional distances in adults and children with ADHD, respectively, could be ascribed to altered DMN consolidation in early ages, yielding to abnormal functional connectivity profiles when compared to age-matched controls. However, a longitudinal study would be needed in order to establish conclusions on the evolution of default mode SFC throughout the lifespan of ADHD patients from childhood into adulthood compared to controls.

The discrepancies between our study and the previous study on SFC in children with ADHD [178] could also be related to medication status. While Carmona *et al.* [178] analyzed brain activity in a mixed sample of medicated and medication-naïve children, our present study comprised medication-naïve adults. As reported by Carmona *et al.* [178], medication status can influence SFC profiles (see Figure 5 in Carmona *et al.* [178]). Moreover, atomoxetine has been found to strengthen the anticorrelation between the DMN and task-positive networks [210], and ADHD medication in general has been proposed to normalize DMN activity [211]. All in all, medication status seems a relevant factor to consider in future studies specifically addressing DMN functional connectivity in ADHD across the lifespan.

4.3. Association with Clinical Scales

At short, medium, and long functional distance, ADHD symptom scores were positively correlated with the degree of functional connectivity between seed regions and regions of the somatosensory-motor and dorsal attention networks. The positive correlation with somatosensory-motor regions is coherent with the increased SFC within sensory cortices in ADHD patients compared to controls. Indeed, children with ADHD also show increased degree centrality, that is, increased number of direct connections with other nodes in the somatosensory cortex [212]. Anatomical studies also point to alterations in somatosensory-motor cortices that persist into adulthood [16]. For instance, studies in children with ADHD report decreased gray matter volume in the somatosensory, motor, and premotor cortices [178], while studies in adults with ADHD found increased cortical thickness in the presupplementary motor area and the somatosensory cortex [213]).

We also found a positive correlation between ADHD symptom severity and SFC in the dorsal attentional network. This finding dovetails with studies pointing to altered within network connectivity in the dorsal attentional network in adults with ADHD [214] and increased connectivity between the dorsal attentional network and regions of the DMN

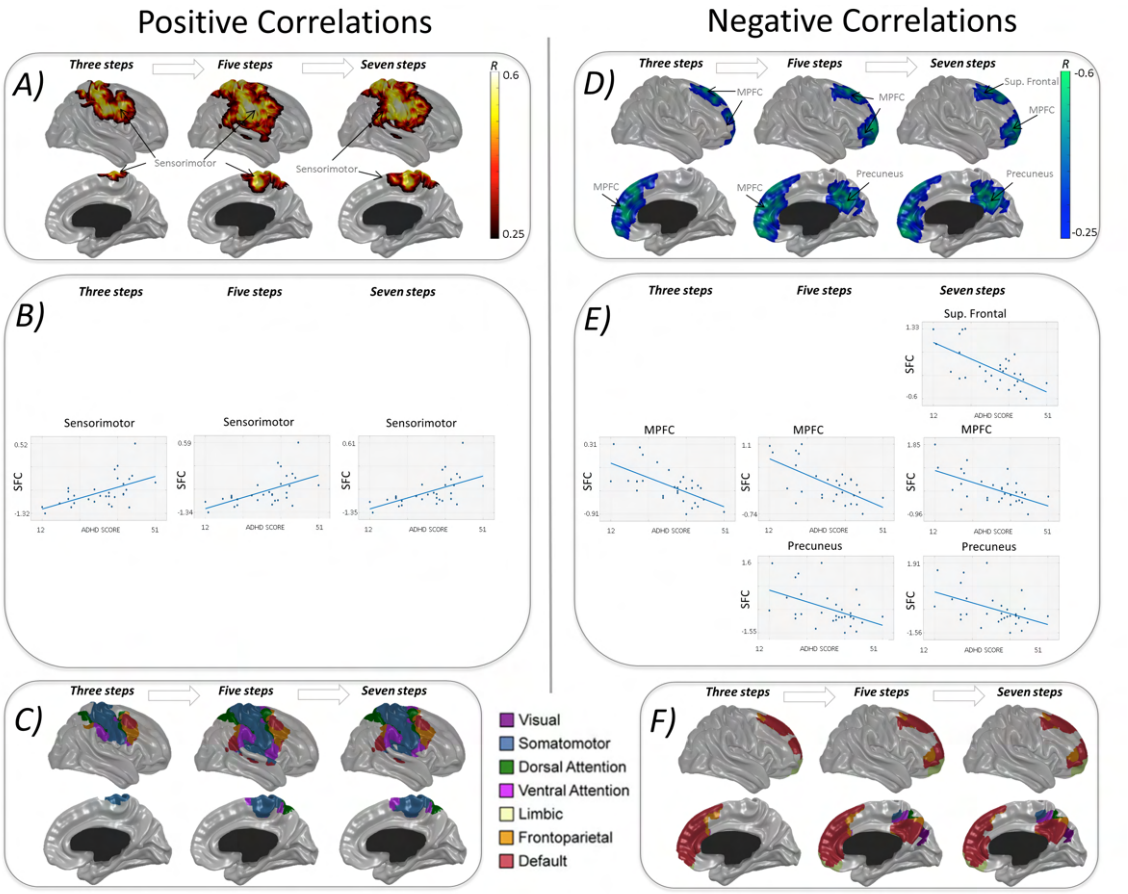


Figure 13: Results of the regression analysis using the ADHD rating scale score as a predictor of stepwise functional connectivity. Subplots (a), (c), and (e) depict positive correlations and subplots (b), (d), and (f) depict negative correlations. Top surface images show the correlation coefficient r at three, five, and seven link-step distances, and the color maps range from r=0.25 absolute value (which corresponds to the minimum [bilateral] significant correlation at p<.05) to r=0.6 absolute value. Subplots (c) and (d) show the scatter plots for the positive and negative correlations, respectively. Bottom surface images (e and f) indicate to which large-scale resting-state functional networks the significant voxels belong according to the parcellation of Yeo et al. (2011). Left hemispheres are displayed. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SFC, stepwise functional connectivity

in medication-naïve children with ADHD [188]. Given the relevance of the dorsal attention network in attentional performance [215], it would be interesting to test whether the increased SFC between seed regions and nodes of the dorsal attention network predicted attentional performance.

Regarding negative correlations, we found that the higher the scores in ADHD symptom severity, the lower the degree of connectivity between the seed regions and the DMN and the frontoparietal network at short, medium, and long functional distance (three to seven link-step maps). These findings are aligned with studies pointing to impaired functioning of the frontoparietal network in ADHD [187, 210, 216–218] but also highlight the relevance of DMN alterations in adult ADHD.

Altogether, our results are consistent with the view that ADHD is associated with altered information flow between sensory and neural nodes supporting higher order cog-

nitive functions: whereas primary sensory areas seem to be hyperconnected in the first steps, they seem to be underconnected to brain regions supporting higher order cognitive functions, especially the DMN, at long functional distances [23]. Our results also point out that, in terms of SFC, the ADHD brain is highly heterogeneous —as indicated by our limited classification accuracy— and suggest that part of this variability might be driven by differences in the severity of ADHD symptoms.

5. Limitations and Conclusions

Limitations

The main limitation of our study is the relatively small sample size with a wide age range. This stems from the difficulty in recruiting ADHD patients who reach adulthood without comorbidity with other disorders (including tobacco and alcohol use in the last 6 months) and, importantly, without previous exposure to ADHD medication.

Also, as our sample exclusively comprised patients with the combined subtype, we could not provide a specific account of what precise ADHD phenotypes are associated with the SFC alterations. The question remains whether impaired sensory-multimodal integration may be affecting attentional control, as well as other symptoms such as hyperactivity and impulsivity. Further research should be able to draw more precise conclusions on what particular phenotypes are linked to which specific SFC alteration.

Regarding methodological concerns, we should specify two. First, computational constraints required us to downsample data to relatively large voxels (4 mm^3). As computational power continues to increase, the specific details of our results could be reexamined in the original data and in future datasets acquired at even greater temporal and spatial resolutions. Second, SFC analysis does not provide information on the directionality of the functional connectivity network under study; that is, the alterations observed could be interpreted as affecting sensory-to-cognitive and/or cognitive-to-sensory information processing. If SFC decrease was affecting sensory-to-cognitive functional streams, this would involve a reduced information feed from sensory up to higher level association nodes; if it was affecting cognitive-to-sensory functional streams, this would entail lower cognitive control over incoming perceptual information —thus hindering selective attention. Hence, although previous studies using SFC analysis tend to interpret their results in the sensory-to-cognitive direction [23, 178, 219], the directionality of the observed alterations should be tested in future studies using methods such as Dynamic Causal Modeling [106].

Conclusions

In this study, we characterized how primary sensory regions interact with networks supporting higher order cognitive functions in adult ADHD by means of an SFC protocol. Furthermore, we ensured that this characterization was biased neither by comorbidities nor by medication. Our results suggest that the brain of adults with ADHD presents an atypical flow of information from short to long functional distances of the sensation to cognition continuum. In particular, SFC in medication-naïve adults with ADHD was characterized by over-connectivity within primary sensory regions followed by under-connectivity between sensory regions and nodes of the DMN. Importantly, this pattern was associated with the severity of ADHD symptoms. These findings highlight the need

to draw greater attention to altered multilevel information processing in adult ADHD, with an emphasis on the interaction between primary sensory regions and the DMN.

Acknowledgements and Conflict of Interest

Acknowledgements

The authors thank the volunteers who generously contributed to this research. This work was supported by the Ministerio de Economía y Competitividad research grant (SAF2012-32362) and the Instituto de Salud Carlos III (Miguel Servet Type I (CP16/00096), AES Grant(PI17/00064), and P-FIS Grant (FI18/00255)).

Conflict of Interest

Dr. Ramos-Quiroga and Dra. Richarte have served on the speakers' bureau and acted as consultant for Eli Lilly and Co., Janssen-Cilag and Shire. Dr. Ramos-Quiroga has also served on the speakers' bureau and acted as consultant for Laboratorios Rubió, Novartis, Lundbeck and Ferrer. Both have received travel awards from Eli Lilly and Co., Janssen-Cilag, and Shire for participating in psychiatric meetings. The ADHD Program has received unrestricted educational and research support from Eli Lilly and Co., Janssen-Cilag, Shire, Rovi, and Laboratorios Rubió in the past two years. The rest of the authors declare no conflict of interest.

STUDY 2

Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder

Marcos-Vidal, L., Martínez-García, M., Pretus, C., Garcia-Garcia, D., Martínez, K., Janssen, J., Vilarroya, O., Castellanos, F. X., Desco, M., Sepulcre, J., & Carmona, S.

Human Brain Mapping (2018)

Abstract

Previous studies have associated Attention-Deficit/Hyperactivity Disorder (ADHD) with a maturational lag of brain functional networks. Functional connectivity of the human brain changes from primarily local to more distant connectivity patterns during typical development. Under the maturational lag hypothesis, we expect children with ADHD to exhibit increased local connectivity and decreased distant connectivity compared with neurotypically developing (ND) children. We applied a graph-theory method to compute local and distant connectivity levels and cross-sectionally compared them in a sample of 120 children with ADHD and 120 age-matched ND children (age range=7–17 years). In addition, we measured if potential group differences in local and distant connectivity were stable across the age range considered. Finally, we assessed the clinical relevance of observed group differences by correlating the connectivity levels and ADHD symptoms severity separately for each group. Children with ADHD exhibited more local connectivity than age-matched ND children in multiple brain regions, mainly overlapping with default mode, fronto-parietal and ventral attentional functional networks ($p<.05$- threshold free-cluster enhancement–family-wise error). We detected an atypical developmental pattern of local connectivity in somatomotor regions, that is, decreases with age in ND children, and increases with age in children with ADHD. Furthermore, local connectivity within somatomotor areas correlated positively with clinical severity of ADHD symptoms, both in ADHD and ND children. Results suggest an immature functional state of multiple brain networks in children with ADHD. Whereas the ADHD diagnosis is associated with the integrity of the system comprising the fronto-parietal, default mode and ventral attentional networks, the severity of clinical symptoms is related to atypical functional connectivity within somatomotor areas. Additionally, our findings are in line with the view of ADHD as a disorder of deviated maturational trajectories, mainly affecting somatomotor areas, rather than delays that normalize with age.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder with an estimated prevalence of up to 9% in school-age children [220]. Its characteristic symptoms are age-inappropriate levels of inattention, hyperactivity and impulsivity that interfere with social and academic functioning [221].

According to neurodevelopmental formulations, ADHD involves a lag in the maturational trajectories of certain brain features [10, 143]. This theory, known as the "maturational lag" hypothesis, has been supported by a series of longitudinal neuroanatomic studies from one group [144, 151–153]. However, current neurobiological models propose that, beyond purely neuroanatomical alterations, the disorder implies altered functional connectivity in several large-scale functional networks [187, 222–224]. Based on the maturational lag hypothesis, researchers have used resting-state functional magnetic resonance imaging (r-fMRI) to investigate whether the functional architecture of the ADHD brain shows signs of atypical or delayed development [154–157]. Despite being based on cross-sectional data, their results are consistent with the view that deviations from the neurotypical patterns of functional connectivity, mainly affecting the default mode and attentional networks, are implicated in both impaired attention performance and ADHD status.

Local and distant functional connectivity profiles have been put forward as predictors of the brain maturity state [225]. From a whole-brain perspective, typical maturational patterns of functional connectivity are characterized by a "segregation" of anatomically close regions (i.e., decrease in correlation strength) and a simultaneous "integration" of distributed regions into mature functional networks (i.e., increase in correlation strength) [139, 226–228]. In consequence, the brain's functional architecture shifts from a local to a more distant distribution as age increases. This organization principle especially affects higher-order cognitive networks (for instance the fronto-parietal, default mode and attentional networks), whose mature-like functional architecture consists of nodes that are spatially distributed across the cortex. However, this pattern does not apply to motor and sensory networks, whose spatial distribution of functional connections remains localized across development [229]. Importantly, such "local to distributed" developmental pattern of functional connectivity remains after controlling for motion parameters [196, 230].

To our knowledge, local and distant functional connectivity profiles have not been used to characterize the maturational state of the brain of children with ADHD. The current study aimed to investigate this question. We cross-sectionally compared the patterns of local and distant functional connectivity between children and adolescents with ADHD and age-matched neurotypically developing (ND) children with the aim of capturing the maturational state of the brain's functional architecture in ADHD. Based on previous findings, we expected to find a less mature functional organization in an ADHD sample compared with age-matched peers as reflected by increased local and decreased distant functional connectivity. In addition, we tested whether connectivity patterns varied across

the age range considered, to discern between delays that eventually normalize and deviations from typical maturational patterns that do not reach normative levels. Finally, we also hypothesized that the degree of local and distant connectivity would be related to severity of clinical symptoms of ADHD.

2. Methods

2.1. Study Participants and Selection of MRI Data

We used a subsample of the ADHD 200 open-source dataset deposited at the Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) platform (https://fcon_1000.projects.nitrc.org/indi/adhd200/). The original dataset was aggregated across eight independent imaging sites and ADHD diagnostic criteria and MRI acquisitions protocols varied somewhat across institutions. The initial dataset was filtered to only include right-handed males (defined as Edinburgh Handedness Inventory ≥0.4 [231]) with an estimated IQ above or equal to 80. Subjects with any history of neurological disease, head trauma, or comorbidity, except for oppositional defiant disorder, learning disorder or specific phobia, were excluded. Since the DSM-IV-TR Hyperactive-Impulsive subtype was underrepresented in the initial dataset, we only included ADHD participants pertaining to the Combined and Inattentive subtypes. Regarding MRI parameters, only participants with an r-fMRI sequence containing at least 120 time points were included and only the first 120 volumes of each individual sequence were selected. By homogenizing the length of the sequence, we assured comparability of data density across individuals. Finally, we re-estimated motion parameters and discarded subjects with a mean frame-wise displacement (FD) exceeding 0.5 mm, as measured by the MCFLIRT tool [198]. Participants in both groups were individually matched 1:1 by age (averaged difference 0.9 months and maximum difference ±4 months) and FD (averaged difference 0.005 mm and maximum difference ±0.1 mm).

Table 4 shows the clinical-demographic characteristics of the study sample remaining after the filtering process. The final sample consisted of 120 right-handed males with DSM-IV-TR diagnosis of ADHD, 67 of them with the Combined subtype (Age: mean=12.4 years, SD=2.4, range=7–17; FD: mean=0.07 mm, SD=0.05) and 53 with the Inattentive subtype (Age: mean=11.6 years, SD=1.9, range=8–15, FD: mean=0.05 mm, SD=0.03), and 120 right-handed ND children (Age: mean=12.0 years, SD=2.3; FD: mean=0.07 mm, SD=0.05). Detailed information about the institution-specific procedures and the identification codes of the matched participants are provided as Supporting Information in a previous study that used the same subsample [178]. Information regarding motion parameters and age for each institution is presented in Supporting Information Table S1.

Informed consent was obtained from parents for all participants and procedures complied with the Institutional Review Boards at respective centers. Although ages ranged from 7 to 17 years, we use the term children throughout the article to refer to the sample, for simplicity.

Characteristic	ND			ADHD		
	N	Mean	SD	N	Mean	SD
ADHD Subtype						
Combined				67		
Inattentive				53		
Age (range 7 to 17)	120	12.03	2.2	120	12.06	2.2
Medication status						
Medicated	NA			31		
Medication-naïve	NA			58		
Co-morbidity						
LD	0			7		
LD, ODD	0			7		
LD, SP	0			1		
ODD	0			18		
SP	2			2		
IQ						
Full Scale	120	114.31	13.5	120	106.8**	13.7
Verbal	97	115.1	14.2	120	110.5*	15.4
Performance	97	110.46	13.6	120	101.33**	14.4
ADHD score						
ADHD-RS						
Total	42	29.29	5.7	55	50.8**	8.2
H/I	42	13.46	3.6	55	22.4**	5.9
Inat	42	15.82	3.8	55	28.36**	3.6
ADHD-CPRS-LV						
Total	39	46.46	7.9	60	70**	6.7
H/I	39	46.87	5.2	60	68.67**	10.9
Inat	39	46.64	7.8	60	69.48**	7.7

Table 4: Clinical-demographic characteristics of children. Abbreviations: N=number of subjects; SD=standard deviation; ND=neurotypically developing children; ADHD=children with attention-deficit/hyperactivity disorder; ODD=oppositional defiant disorder; LD=learning disorder; SP=specific phobia; IQ=estimated intelligence quotient; ADHD-RS=ADHD rating scales–IV [232]; H/I=Hyperactive/Impulsive symptoms subscale; Inat=Inattention Symptoms subscale; ADHD-CPRS-LV=Conners' parent Rating Scale-Revised=Long version [189]. For 15 subjects, the IQ was assessed by means of the two subtest (vocabulary and matrix reasoning) form of the Wechsler Abbreviated Scale of Intelligence. [a] Significant between-group differences based on 2-sample t tests (p<.05). **Significant between-group differences based on 2-sample t tests (p<.001).

2.2. Image Processing

The imaging data used in the present study had been already processed by the Neuro Bureau (http://www.neurobureau.org/) and were available in the NITRC platform. Preprocessing was done using AFNI (http://afni.nimh.nih.gov/afni) and FSL (http://fsl.fmrib.ox.-

ac.uk/fsl/fslwiki) neuroimaging toolkits on the Athena computer cluster at the Virginia Tech Advanced Research Computing center (http://www.arc.vt.edu/). Preprocessing steps included the removal of the first four volumes, slice timing correction, motion correction, spatial normalization to MNI152 stereotactic space at 4 mm isotropic voxel resolution, regression of nuisance covariates using head-motion parameters, global mean, white matter, and cerebrospinal fluid signals as regressors, band-pass-filter of the time-series data (0.009–0.08 Hz), and spatial smoothing with a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel. For more details about the image processing pipeline, see: "http://www.nitrc.org/plugins/mwiki/index.php/neurobureau:AthenaPipeline".

Motion artifacts are a primary concern in the study of distance-dependent functional connectomics [195–197, 230]. Therefore, in addition to matching the groups on movement parameters, we applied the method of data censoring or scrubbing by eliminating volumes with FD exceeding 0.5 mm together with the volume acquired immediately after from the time series. A detailed and formal description of this motion correction strategy is provided elsewhere [199, 233]. Finally, a resting-state functional connectivity quality control plot was generated to assess the impact of subject motion on functional connectivity correlations before and after scrubbing, using mean FD as the motion index. Supporting Information Figure S1 shows the distribution of censored volumes across our sample and the effectiveness of the scrubbing procedure.

2.3. Local and Distant Degree Functional Connectivity Measures

The local-distant functional connectivity technique is a graph–theory-based method previously used on r-fMRI data [182]. The method measures local and distant functional connectivity respectively by computing the degree of connectivity of voxels taking into account the distance between them. Degree of connectivity of a given voxel is defined as the number of voxels functionally connected to that target voxel. Briefly, we first obtained a whole brain connectivity matrix for each subject, which is an N by N matrix (where N is the number of voxels) containing the Pearson correlation of the time courses of every voxel with any other voxel in the brain. This matrix was binarized by replacing correlations higher than 0.25 by ones and the rest by zeros, following the criteria described in the original paper [182]. Negative correlations were discarded given that the pre-processing step of global signal regression biases the distribution of connectivity values downwards, thus introducing negative correlations that were not originally present in the data [200, 201]. We calculated the degree of functional connectivity across the brain by introducing a physical distance restriction in the functional connectivity network across the brain. Local connectivity maps were computed as the degree of connectivity within the 28 ×28×28 mm^3 cube surrounding that voxel [182]. For the distant connectivity maps we computed the degree of connectivity of every voxel with those outside their neighborhood (i.e., outside the 28×28×28 mm^3 cube).

For both functional connectivity maps, we adjusted each voxel's degree of functional

connectivity according to the total number of voxels to which it could be connected. This allowed us to correct for voxel position, since voxels located on the borders have part of their surrounding cube outside the brain and have less potential local connectivity and therefore more potential distant connectivity.

The corrected distant functional connectivity value $\hat{d}_i$ was calculated using the following formula:

$$\hat{d}_i = \frac{d_i}{D_i}$$

Where d_i is the distant functional connectivity value of the ith voxel and D_i is the number of voxels out of the ith voxel's cube that fall inside the brain mask, so that $\hat{d}_i$ varies from 0 to 1.

Respectively, the corrected local functional connectivity value $\hat{l}_i$ was calculated using the following formula:

$$\hat{l}_i = \frac{l_i}{L_i}$$

Where l_i is the local functional connectivity value of the ith voxel and L_i is the number of voxels of the ith voxel's cube that fall inside the brain mask, so that $\hat{l}_i$ varies from 0 to 1.

2.4. Statistical Analysis

Characterizing Local and Distant Functional Connectivity in Children

To examine local and distant connectivity patterns in children with and without ADHD, and visually compare the results to local and distant adult's maps obtained by Sepulcre *et al.* [182], we transformed the mean group local and distant connectivity maps to group specific Z-score maps using the following formula:

$$z_i = \frac{x_i - \bar{x}}{\sigma_x}$$

Where z_i is the Z-score of voxel i, x_i is its local or distant connectivity value, $\bar{x}$ is the mean local or distant connectivity value of the whole brain and σ_x is the standard deviation of whole brain local or distant connectivity value. This transformation was performed only for visualization purposes and not for the subsequent analyses, where local and distant connectivity values were used.

Linear Model

Two General Lineal Models were fitted, one for local and one for distant functional connectivity maps. These models included as covariates site, individual mean FD (mean centered to zero) and age (mean centered to zero). For each model, specific contrasts were performed to test group differences and age by group interaction effects. Analyses were performed with SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12; version 95 of September 12, 2016). We used a toolbox for SPM developed by Christian Gaser (http://dbm.neuro.uni-jena.de/tfce) that calculates non-parametric permutation testing (5,000 permutations) based on threshold free-cluster enhancement (TFCE) [234], to obtain both uncorrected and family-wise error (FWE) corrected p-values. The maps obtained were thresholded at different p-values (p<.05-TFCE, p<.01-TFCE, p<.005-TFCE, and p<.05 TFCE^{FWE} corrected) to have a wide overview of results. This allowed us to observe the distribution of differences across the brain with varying levels of certainty, although we considered as significant only those clusters with voxels below p<.05-TFCE–FWE.

Finally, to understand how the differences in local connectivity were distributed across large-scale networks, we calculated the percentage of voxels that pertained to each of the seven cortical and subcortical large-scale resting-state functional networks described by Thomas Yeo *et al.* [19] and Choi *et al.* [235]. Percentages were calculated over the total number of significant voxels at the most lenient threshold (p<.05-TFCE), thus warranting a broad characterization of the potentially affected large-scale networks.

Correlations with Clinical Symptoms

Regression analyses were performed to test the associations between local and distant functional connectivity and severity of ADHD symptoms. The analyses were performed separately for the ADHD sample and the ND sample and were restricted to the regions that differed significantly between groups (p<.05-TFCE). Different sites used different scales to measure the severity of ADHD symptoms (see the Section 2.1). To reduce the overall heterogeneity associated with the use of different clinical scales, only those sites with the larger samples were considered (i.e., New York University [NYU] and Peking University [PU]; Supporting Information Table S1) and regressions were fitted for each of the sites separately.

Two General Lineal Models were fitted, one for local and one for distant functional connectivity differences, that included as covariates the score on the ADHD clinical scale (ADHD score), individual mean FD (mean centered to zero) and age (mean centered to zero). Since these were masked analyses, the TFCE spatial correction was not appropriate. The masked maps were then thresholded at the same p-values employed in the group comparisons (p<.05, p<.01, p<.005, and p<.05 FWE corrected). FWE correction was applied via a non-parametric permutation analysis implemented in Matlab (5,000 permu-

tations). To additionally control for false positives, we considered as “statistically valid” only those regions whose voxels overlapped between the NYU and the PU sites.

3. Results

3.1. Characterization of Local and Distant Functional Connectivity Maps in ND Children and in Children with ADHD

Figure 14 displays the local and distant functional connectivity maps for the ND and the ADHD groups. For comparison purposes, we also incorporated the functional connectivity maps calculated by Sepulcre *et al.* [182] in an adult sample. Visual inspection of the results suggests that the distribution of local and distant functional connectivity is more similar between the child samples, regardless of diagnosis, than between children and adults.

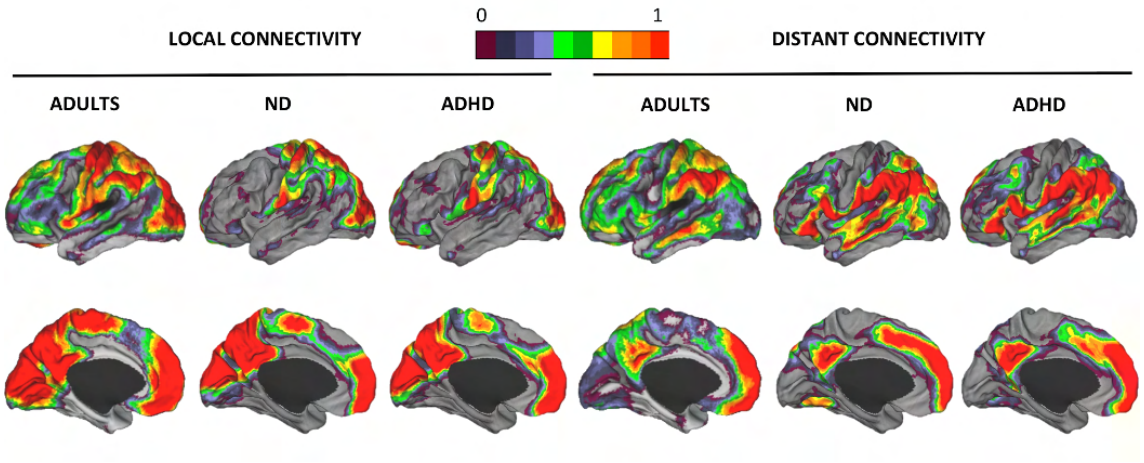


Figure 14: One-sample characterization of local and distant functional connectivity levels. Local and distant functional connectivity Z-score maps in adults, ND children, and children with ADHD. Lateral and medial views of the left hemisphere are presented. Surface projection used the PALS surface (PALS-B12) provided by Caret software using the "interpolated algorithm" and "multifiducial mapping" settings [236]. The color bar represents the normalized Z-scores. Only positive Z-score values are plotted, 0 corresponding with a Z-score value of 0 and 1 corresponding with Z-score values 1. Local and distant adult's maps were taken from a previous study [182]. The color spectrum was the same used by Sepulcre *et al.* [182] to make the images comparable

3.2. Group Differences in Local and Distant Maps Between Children with ADHD and ND Children

As displayed in Figure 15 and Table 5 widespread regions that include cortical and subcortical areas. When examined in terms of large-scale functional parcellations [19, 235], increases in local functional connectivity fell into the somatomotor, fronto-parietal, default mode, visual and attentional networks. The two clusters of increased local functional connectivity surviving the most restrictive threshold (p<.05-TFCE^{FWE}) were regions overlapping with the default mode, fronto-parietal and ventral attentional functional

networks. As post-hoc analysis, we measured to which extent these increases in local connectivity resulted from increased connectivity among different functional networks that were spatially contiguous. For that purpose we created two extended masks, each one including not only the voxels of the two significant clusters (p<.05-TFCE^{FWE}) but also the neighboring voxels that were used to calculate their degree of local connectivity. Results indicated that one of the extended masks was comprised by voxels of the default mode (80%), fronto-parietal (14%) and ventral attentional (6%) functional networks. Similarly, the other extended mask was comprised by voxels of the ventral attentional (72%), fronto-parietal (16%), somatomotor cortex (10%), and default mode (3%) functional networks.

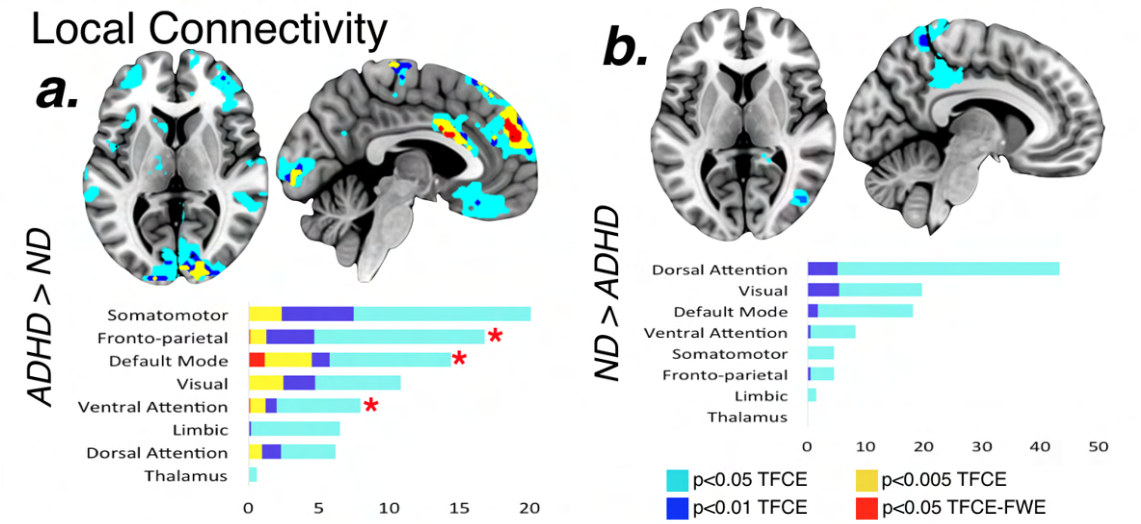


Figure 15: Group differences in the degree of local functional connectivity. Differences in local functional connectivity between children with ADHD and ND children. (a) Regions where patients with ADHD have more local functional connectivity compared with ND children; (b) Regions where patients with ADHD have less local functional connectivity compared with ND children. The results have different colors for different thresholds and bar graphs represent the percentage of voxels in each of the large-scale functional networks over the total significant voxels under the most lenient threshold of p<.05-TFCE. Red asterisks represent the clusters of increased local functional connectivity surviving the most restrictive threshold corrected for multiple comparisons (p<.05-TFCE^{FWE})

Considering the ND>ADHD contrast (Figure 15 and Table 5), children with ADHD exhibited a decrease in the degree of local functional connectivity within the secondary visual cortex and the superior parietal cortex extending into the precuneus (p<.01-TFCE). With respect to the distant functional connectivity maps, group differences were scarce and the majority only survived the most lenient threshold of p<.05-TFCE (Table 5). Patients with ADHD showed decreased distant functional connectivity in the bilateral cerebellum, right superior frontal gyrus, right posterior cingulate gyrus, and in right parahippocampal regions extending into the visual cortex.

	Cluster size (mm^3)	x (mm)	y (mm)	z (mm)	TFCE	p-value
LOCAL CONNECTIVITY						
ADHD>ND						
Right Superior Frontal Gyrus Medial	139136	4	54	31	255.26	0.001*
Right Occipital Pole/Right Calcarine Cortex	25856	20	-92	5	216.56	0.002
Right Middle Frontal Gyrus/ Right Opercular part of the Inferior Frontal Gyrus	9152	36	9	26	201.60	0.002
Left Medial Orbital Gyrus/Left Anterior Cingulate Gyrus	10816	-12	30	-15	142.33	0.007
Right Middle Temporal Gyrus	6848	48	-37	2	138.80	0.008
Right Parietal Operculum/ Right Transverse Temporal Gyrus	8384	36	-27	17	136.93	0.008
Left Anterior Insula	2112	-32	24	2	113.34	0.015
Right Parahippocampal Gyrus	448	16	-10	-24	100.29	0.021
Left Entorhinal Area	3776	-28	1	-37	98.54	0.022
Left Temporale Pole	832	-52	9	-37	87.34	0.030
Right Lingual Gyrus/ Right Precuneus	1856	4	-56	7	86.80	0.030
Left Caudate	1216	-8	16	6	80.10	0.036
Left Thalamus Proper	1280	-8	-17	0	78.23	0.038
Left Angular Gryrus	768	-44	-66	44	76.87	0.040
Left Middle Temporal Gyrus	512	-64	2	-21	75.31	0.042
ND>ADHD						
Right Posterior Cingulate Gyrus/ Right Precuneus	512	20	-44	10	169.34	0.125
Right Middle Occipital Gyrus/ Right Inferior Occipital Gyrus	4160	44	-72	12	167.04	0.130
Right Precuneus/ Right Superior Parietal Lobule	15808	4	-48	75	163.59	0.137
Left Inferior Temporal Gyrus	320	-52	-19	-31	94.26	0.438
DISTANT CONNECTIVITY						
ND>ADHD						
Right Posterior Cingulate Gyrus	896	20	-44	6	168.84	0.006
Right Fusiform Gyrus/ Right Inferior Temporal Gyrus	2048	44	-26	-19	141.92	0.012
Right Superior Frontal Gyrus	192	24	20	62	119.50	0.019
Right Hippocampus	384	32	-33	-3	98.20	0.031
Right Cerebellum Exterior	448	16	-67	-36	92.27	0.036
Left Cerebellum Exterior	384	-28	-64	-40	89.99	0.038

Table 5: Group differences in LFC in children. Coordinates are based on MNI152 stereotactic space. Results reported in the table correspond to those clusters above 192 mm^3 (three contiguous voxels). Abbreviations: ADHD=children with attention-deficit/hyperactivity disorder; ND=neurotypically developing children. TFCE=threshold-free cluster enhancement; FWE=family-wise error. [a]Significant at p<.05 $TFCE^{FWE}$ level.

3.3. Group by Age Interaction

Regarding the group by age interaction analysis, we did not find any significant result at the most restrictive threshold of p<.05-$TFCE^{FWE}$. Table 6 and Figure 16 show the results at a more lenient level of p<0.005-TFCE. In particular, we found that whereas the local connectivity in left somatomotor region, left thalamus and cerebellum decreased with age in ND children, it increased with age in children with ADHD (Figure 16). Of notice, the peak of the cluster comprising the left somatomotor cortex almost survived the $TFCE^{FWE}$ correction for multiple comparisons (TFCE=217.03; p=.051-$TFCE^{FWE}$).

3.4. Clinical Correlations

No significant clinical correlations were found at p<0.05-FWE. We found several clusters whose local connectivity significantly correlated with the severity of ADHD symptoms at p<.005 (Table 7). Figure 17 displays the results for the NYU and PU samples separately at the most lenient threshold of p<.05 and indicates the voxels that overlap between the

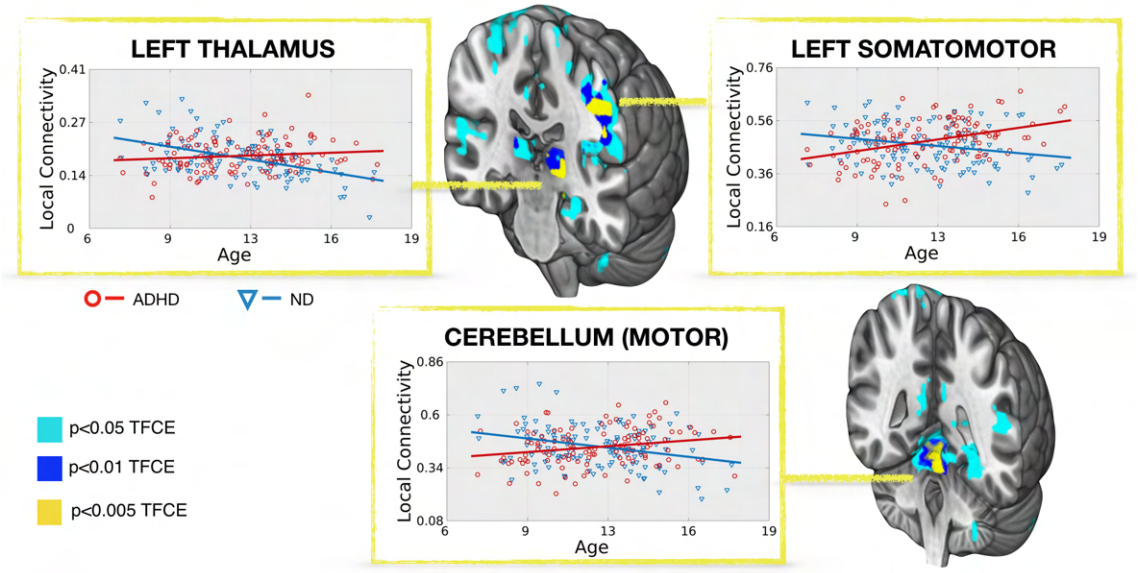


Figure 16: Group by age interaction. Regression between age and the degree of local functional connectivity in children with ADHD and ND children. 3D coronal views display the regions where the degree of local connectivity increases with age in children with ADHD while decreases with age in ND children. The x-axis shows the age of the subjects and the y-axis represents the mean degree of local connectivity of the region after removing the effect of site and FD. The local connectivity values are in the normalized scale detailed in methods (from 0 to 1). The results have different colors for different thresholds.

two sites. For both sites and both samples, higher scores on the ADHD clinical scales were associated with higher local functional connectivity in regions that mainly involve the somatomotor network. Indeed, when we tested which voxels overlapped between the two sites, we noticed that all the overlapping voxels fell into areas that belong to the somatomotor functional network.

4. Discussion

This study cross-sectionally compared the patterns of local and distant functional connectivity between a sample of children with ADHD and a sample of ND children. We found that children with ADHD exhibited more local functional connectivity than ND children in multiple brain networks. Given the local to distant trend during functional network development, our results point to a more immature functional connectivity profile in ADHD compared with ND children.

Despite the traditional view of ADHD involving alterations in discrete circuits of the brain [87, 237, 238], recent neurobiological models are tending to multinetwork explanations [170, 187, 239]. Broadly speaking, r-fMRI studies have reported decreased integration among distributed regions within a network and decreased segregation between distinct networks in ADHD [21, 167, 177, 185, 205]. Considering the typical functional trajectories of the human brain [196, 229], these findings suggest that functional networks may not have been properly consolidated during development. Therefore, from a neurodevelopmental perspective, the atypical functional connectivity affecting multiple large-scale brain networks in ADHD could be understood as a deficient level of maturation. Among previous r-fMRI studies, that of Tomasi and Volkow [163] is the most closely related to ours at the methodological level. Short- and long-range functional connectivity alterations in patients with ADHD have been reported, specifically in short-range connectivity of reward/motivation regions and decreases in the short and long-range functional connectivity of the default mode and the dorsal attentional networks [163]. It is difficult to disentangle the extent to which the group differences reported by Tomasi and Volkow [163] reflect immaturity traits of the ADHD brain since their groups differed significantly in age. Conversely, the current study used a more homogeneous age-matched sample, thereby bypassing confounding effects of age and facilitating inference of between-group maturational differences. We also found notable increases in local functional connectivity in the ADHD sample while no significant differences in distant functional connectivity were detected.

Among the distributed pattern of local functional connectivity increases in ADHD, the regions that survived multiple comparison correction overlapped with regions pertaining to the default mode, fronto-parietal and ventral attentional networks. Although atypical local functional connectivity levels are not necessarily related to the interplay among functional networks, the ADHD literature has described alterations in the interactions among such networks. Extending the "default-mode interference" model [13], Menon [14] proposed that default mode interferences during externally focused cognition may be caused by an impaired regulation of the ventral attentional network over the interplay between the default mode and executive networks (mainly the fronto-parietal network). Atypical interconnectivity among these cooperative networks has been found in ADHD by independent groups [21, 167, 177, 185]. Overall, these findings are consistent with ours, suggesting an immature pattern of functional connectivity in ADHD mainly affect-

	Cluster Size (mm^3)	x (mm)	y (mm)	z (mm)	Network	TFCE	*p*-value
LOCAL CONNECTIVITY							
Increases with age in ADHD & Decreases in ND							
Left Postcentral Gyrus	35584	-44	-22	41	DAN	217.03	0.002
Cerebellar Vermal Lobules	52480	0	-46	-14	SN	194.55	0.003
Right Superior Temporal Gyrus	6656	56	-13	0	SN	129.26	0.010
Right Superior Parietal Lobule	17024	28	-65	56	DAN	126.85	0.011
Left Frontal Pole	16000	-28	64	3	DMN	111.35	0.016
Right Middle Cingulate Gyrus	5632	4	-2	35	VAN	106.83	0.018
Left Cerebellum	3968	-16	-87	-27	DMN	95.28	0.025
Left Anterior Cingulate Gyrus	3840	-4	39	-4	DMN	94.47	0.025
Right Anterior Insula	3392	44	11	-10	SN	93.19	0.026
Right Supplementary Motor Cortex	192	12	-10	44	SN	91.03	0.028
Left Superior Frontal Gyrus	448	-20	57	19	DMN	82.06	0.035
Right Supplementary Motor Cortex	1088	4	16	62	VAN	76.22	0.042
Left Parahippocampal Gyrus	384	-28	-15	-32	Limbic	76.12	0.042
Left Cerebellum	192	-36	-67	-32	FPN	75.45	0.043
Left Cerebellum	448	-32	-44	-42	FPN	74.64	0.045
Right Superior Temporal Gyrus	320	64	7	-2	SN	74.60	0.045
Right Lateral Orbital Gyrus	256	44	47	-12	FPN	71.89	0.047
Right Precuneus	192	4	-54	43	DMN	70.34	0.050
DISTANT CONNECTIVITY							
Increases in ND & Decreases in ADHD							
Right Supramarginal Gyrus	448	60	-46	38	FPN	103.7	0.03

Table 6: Group by age interaction. Effect of the interaction of age and group differences in the degree of local and distant connectivity. Coordinates are based on MNI152 stereotactic space. Results reported in the table correspond to those clusters above 192 mm^3 (three contiguous voxels). Abbreviations: ADHD=children with attention-deficit/hyperactivity disorder; ND=neurotypically developing children; TFCE=threshold-free cluster enhancement. [a]FWE-corrected p-value=.051.

ing the triple cognitive network model comprising the default mode, fronto-parietal and ventral attentional networks [14].

It is important to remark that differences surviving stringent multiple-comparison correction in regions of the default mode, fronto-parietal and ventral attentional functional networks do not necessarily imply that alterations are restricted to these networks. Rather, we propose that our results should be understood within the context of an immature state of functional connectivity affecting multiple brain regions, including default mode, fronto-parietal and attentional regions, but also visual, somatomotor and basal ganglia regions.

Whereas the functional networks that support higher-order cognitive functions present a distributed topography, networks sustaining sensory and motor processing consist of a single area of functionally connected contiguous voxels [229]. Therefore, our findings pointing to an increased local connectivity in the visual and somatomotor cortices would likely indicate increased within-network integration. In contrast, the increased local connectivity found in the anterior part of the medial wall, an area where the default mode, fronto-parietal and ventral attentional networks are highly intertwined, would likely reflect increased integration between these typically segregated networks. Indeed, our post-

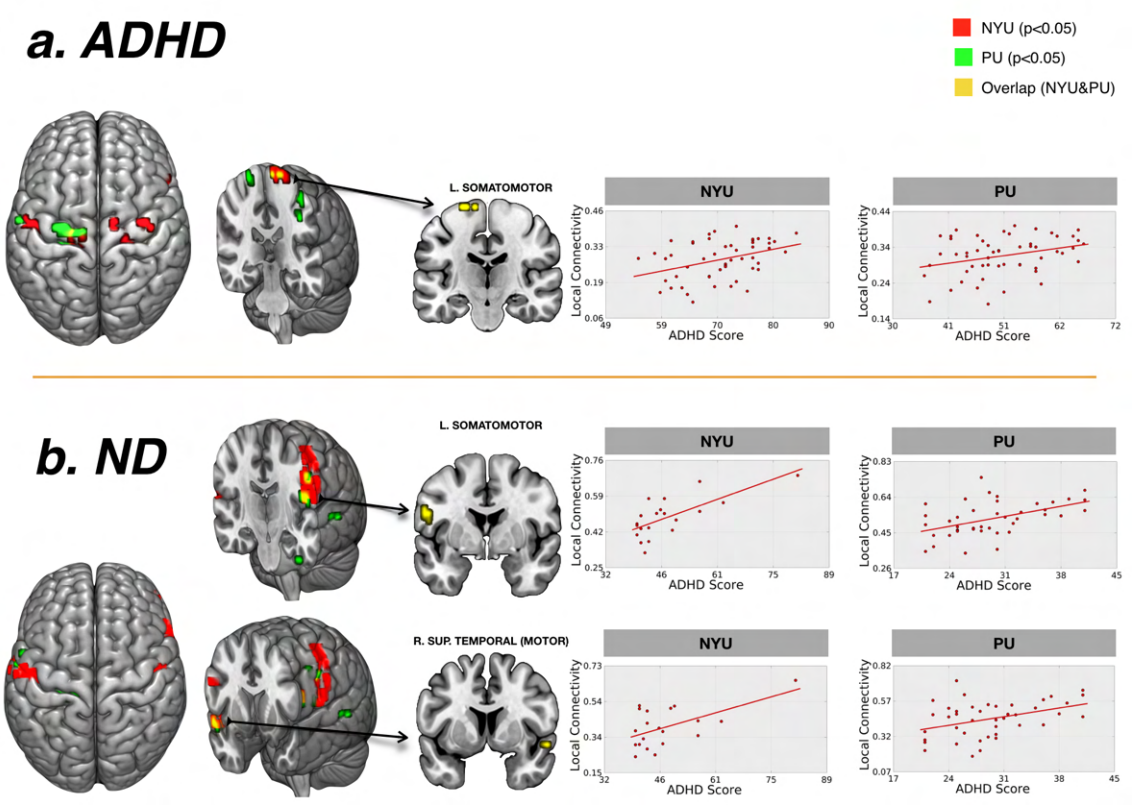


Figure 17: Correlations with clinical measures. Results of the regression analysis between the degree of local functional connectivity and ADHD clinical scores. The y-axis represents the mean degree of local functional connectivity of the region after removing the effect of age and FD. The x-axis represents ADHD clinical severity score (based on the ADHD Rating Scale (ADHD-RS) score for PU; and based on the Conners' Parent Rating Scale-Revised, Long version (CPRS-LV) score for NYU). The local connectivity values are in the normalized scale detailed in methods (from 0 to 1). Results presented correspond to those voxels below an uncorrected $p<.05$ obtained in the NYU, PU, and both sites (displayed in red, green and yellow colors respectively). L: left hemisphere; R: right hemisphere; ND, neurotypically developing children.

hoc analysis confirmed that the local connectivity increases found in the cingulate and medial prefrontal cortex fell into the boundaries confining the default mode, fronto-parietal and ventral attentional networks. Previous literature in ADHD reports increased within-network connectivity in motor [176, 178] and visual regions [135, 175, 177, 178], and decreased within-network integration [167, 205] and between-network segregation in networks associated with higher-order cognitive processes [21, 177, 185]. In the light of our results, it is possible that previous studies reporting atypical integration and segregation patterns reflect, in part, more locally connected brains that manifest differently depending on the topological organization of the network.

As previously mentioned, we did not find evidence for altered distant functional connectivity. We believe this indicates that distant connections are preserved in the disorder. However, in this study we only considered positive correlations to avoid the ambiguous interpretations of the correlation sign after removal of mean global signal [182, 200, 201]. Therefore, another possibility is that abnormalities in distant connections are driven

by negative correlations, in keeping with studies reporting decreased segregation between typically anti-correlated networks in ADHD [21, 177, 185], and have remained undetected in our study.

Region	Cluster Size	x	y	z	*t* statistic	Network
NYU						
Control						
Right Superior Temporal Gyrus	5	56	3	-9	3.970	DMN
Postcentral Gyrus	28	-52	-8	16	3.773	SN
Left Precentral Gyrus	8	-52	1	31	3.021	SN
Left Amygdala	5	-24	-24	-25	2.596	DMN
ADHD						
Right Insula	28	44	3	-5	3.641	VAN
Left Precentral Gyrus	43	-24	-20	73	3.514	SN
Right Anterior Cingulum	14	8	36	13	2.974	DMN
Right Superior Occipital	7	20	-92	5	2.853	VN
Right Postcentral	18	44	-33	53	2.835	DAN
Left Frontal Superior	8	-16	23	58	2.718	DMN
Left Postcentral	10	-56	-13	48	2.689	SN
Right Middle Cingulum	6	0	6	43	2.243	VAN
PU						
Control						
Left Postcentral	23	-48	-14	32	3.533	SN
Right Superior Temporal	18	52	-1	-5	3.448	SN
Right Calcarine	8	16	-80	5	2.466	VN
ADHD						
Left Precentral	71	-16	-16	68	4.046	SN
Right Inferior Frontal Operculum	6	36	22	30	3.898	FPN
Right Superior Motor Area	8	4	-8	60	3.353	SN
Left Middle Frontal	8	-32	37	17	3.334	FPN
Right Temporal Inferior	7	60	-34	-19	3.099	FPN
Right Precentral	39	20	-20	69	3.081	SN
Right Superior Frontal	8	16	56	11	2.903	FPN
Right Inferior Parietal	9	44	-57	47	2.622	DMN
Left Middle Frontal	5	-36	52	4	2.473	FPN

Table 7: Clinical Regression with LFC in children. Coordinates are based on MNI152 stereotactic space. Results reported in the table correspond to those clusters above 192 mm^3 (three contiguous voxels). Abbreviations: ADHD=children with attention-deficit/hyperactivity disorder; ND=neurotypically developing children; TFCE=threshold-free cluster enhancement. [a]FWE-corrected p-value=.051.

Regarding clinical correlations, we found that regions of the somatomotor functional network exhibited a positive correlation between local functional connectivity levels and ADHD clinical symptoms. Interestingly, this association was observed both in the patient and control groups and replicated in two independent samples. Several studies using dif-

fusion tensor [240, 241], structural [242], functional [243] and resting state analyses [178, 244] support the involvement of somatomotor circuitry in the pathophysiology of ADHD. Our data also support this association and suggest that the atypical degree of somatomotor local functional connectivity might be understood as a continuum independently of diagnosis.

Regarding the effect of age, it remains a matter of debate whether the immaturity features observed in ADHD reflect a delay with potential for latter normalization or a deviation of normative developmental trajectories. We found that group differences in functional connectivity did not reduce across the age range of our samples. In particular we found that the developmental trajectories of the somatomotor cortex significantly differed between the groups. Therefore, our results do not support the hypothesis that brain immaturity features in children with ADHD normalize with age, in contrast with initial longitudinal reports on anatomical trajectories [144, 153]. However, as in our case, r-fMRI studies reporting functional connectivity abnormalities compatible with a less mature state in ADHD did not find evidence that such alterations reach normative levels as age increases [154–156, 177]. All that being said, the cross-sectional design of these studies, including that of the current work, prevents us from drawing strong conclusions about the shape of a developmental trajectory. Future studies collecting longitudinal r-fMRI data are required to test if the trajectories of functional connectivity in patients with ADHD are linearly modulated by age or instead follow a non-linear pattern of development.

5. Limitations and Conclusions

Limitations

In addition to the cross-sectional design, other considerations should be taken into account when interpreting the present findings. First, the sample was aggregated from different sites and scanners, with different image acquisition parameters and different clinical measures. We tried to address this limitation by including scanner site as a nuisance covariate in the analyses and by examining the NYU and PU clinical data separately. Second, given the controversial interpretation of negative correlations after mean global signal regression [200, 201], the method used in the current study was designed to only capture correlations that exceeded a positive threshold [182]. Therefore, potential differences related to negative functional correlations could have been missed by this approach. Third, controlling for in-scanner head motion was of particular importance in the present study given that (1) our sample of study is characterized by high hyperkinesia, which can introduce motion artifacts on MRI data [245]; and (2) distance-dependent functional connectivity analysis is especially sensitive to motion influence, that is, it inflates the correlation among neighboring voxels while weakening that of those voxels that are wider apart [195–197, 230]. For that reason, we carefully accounted for head motion through several approaches, for example, rigorously matching the subjects by motion and age, censoring high-motion volumes by means of scrubbing and introducing individual mean FD as a covariate in the linear model. These motion correction strategies, together with the fact that we computed the degrees of local and distant connectivity largely in parallel, make it unlikely that the reported effects reflect motion artifacts.

Conclusions

In conclusion, we cross-sectionally compared the local and distant levels of functional connectivity in children with ADHD and ND children. We found a pattern of increased local functional connectivity in regions that have been related with multiple brain networks in functional atlases [19, 235]. On the one hand, these findings extend the view that ADHD involves deficits in several functional large-scale networks. On the other hand, our results suggest that such alterations could be interpreted as an immature state of functional connectivity patterns in ADHD, that is, children with ADHD exhibit more local functional connectivity than their age-matched ND peers. Additionally, our findings are more in line with the view that ADHD is a disorder of deviant maturational trajectories rather than a delay with subsequent age-related normalization.

Acknowledgements

Susanna Carmona is supported by Miguel Servet program of the Instituto de Salud Carlos III (CP16/00096). The authors thank the Neuro Bureau, the ADHD-200 Consortium, Virginia Tech ARC and the Neuroimaging Informatics Tools and Resources Clearinghouse for collecting, organizing, processing and hosting the data used in the present study. We also thank the entities that funded the original studies, especially the Stavros S. Niarchos Foundation, the National Institute of Mental Health (NIMH; R01MH083246) and the Leon Lowenstein Foundation, which supported the NYU Child Study Center subsample; and the National Natural Sciences Foundation of China (NSFC; 30970802), the Commonweal Sciences Foundation, Ministry of Health, China (200802073) and the National Foundation, Ministry of Science and Technology, China (2007BAI17B03), which supported the PU subsample. The authors acknowledge the children and parents who generously contributed to this research. In addition, we want to thank an anonymous reviewer for his/her carefully reading of the manuscript and helpful comments and suggestions, which helped us to significantly improve the quality of the article. Last, the authors do not have conflicts of interest to declare.

STUDY 3

Local Functional Connectivity as a Parsimonious Explanation of the Main Frameworks for ADHD in Medication-Naïve Adults

Marcos-Vidal, L., Martínez-García, M., Martín de Blas, D., Navas-Sánchez, F. J., Pretus, C., Ramos-Quiroga, J. A., Richarte, V., Vilarroya, Ó., Sepulcre, J., Desco, M., & Carmona, S. Journal of Attention Disorders (2022)

Abstract

Objective: Neuroimaging studies in children with ADHD indicate that their brain exhibits an atypical functional connectivity pattern characterized by increased local connectivity and decreased distant connectivity. We aim to evaluate if the local and distant distribution of functional connectivity is also altered in adult samples with ADHD who have never received medication before. Methods: We compared local and distant functional connectivity between 31 medication-naïve adults with ADHD and 31 healthy controls and tested whether this pattern was associated with symptoms severity scores. Results: ADHD sample showed increased local connectivity in the dACC and the SFG and decreased local connectivity in the PCC. Conclusion: Results parallel those obtained in children samples suggesting a deficient integration within the DMN and segregation between DMN, FPN, and VAN. These results are consistent with the three main frameworks that explain ADHD: the neurodevelopmental delay hypothesis, the DMN interference hypothesis, and multi-network models.

1. Introduction

ADHD is one of the most common neurodevelopmental disorders. Its core symptoms include inappropriate developmental levels of inattention, hyperactivity/impulsivity, or a combination of these two symptom domains [25]. ADHD has an estimated prevalence of 9% in the school-age population [220]. However, almost one-third of children with the disorder still fulfill DSM-V diagnostic criteria when they reach adulthood [183, 246, 247]. Compared to studies with children samples, studies of adults with ADHD are particularly scarce in scientific literature.

Currently, results from Magnetic Resonance Imaging (MRI) studies in children support three main neurobiological models of ADHD [170]: the neurodevelopmental delay hypothesis, the Default Mode Network (DMN) interference hypothesis, and the more recent multi-network models. The neurodevelopmental delay hypothesis [10] postulates that ADHD is characterized by neurobiological features that resemble those of a less mature brain, which may remit with time or not [144, 152–154, 207]. The DMN interference hypothesis [13] suggests that the brain of patients with ADHD does not adequately suppress this functional network during periods of active processing, and that this deficient suppression is related to the attentional lapses that characterize ADHD symptomatology [22, 167–169]. Finally, recent multi-network models propose that the disorder results from an atypical functional connectivity within and between several large-scale networks [170, 187], including basic sensorimotor [16, 162, 175–177], and higher-order cognitive circuits [14]. While no one has proposed an underlying process able to encompass these models, we believe that their alterations could be related to abnormalities in local and distant brain functional connectivity patterns.

During development, functional connectivity (FC) shifts from being locally connected, that is, connected to anatomically close areas, to establish distant connections and form large-scale functional networks [139]. Thus, by analyzing the patterns of local and distant functional connectivity at a whole-brain level we can test whether the brains of adult patients with ADHD show features resembling those of a typically less mature brain (increased local connectivity). This methodology also allows us to test whether alterations in local and distant connectivity are restricted to the DMN or also affect other networks. To date, local and distant FC patterns have only been explored in children with ADHD [16, 163]. According to these studies, children with ADHD show signs of brain immaturity that affect mainly, but not exclusively, regions of the DMN. Specifically, they found increased local connectivity patterns in children with ADHD in areas pertaining to the DMN as well as to the fronto-parietal and ventral attentional networks (Anterior Cingulate Cortex and Superior Frontal Gyrus) and the limbic network (Orbitofrontal Cortex and Ventral Striatum). In adults with ADHD, local and distant FC patterns remain unexplored.

In this work, we aim to evaluate local and distant functional connectivity patterns in adults with ADHD by cross-sectionally comparing the local and distant connectivity values of a sample of 31 adults with ADHD with a sample of 31 healthy controls (HC).

Importantly, all our ADHD subjects were medication-naïve, thus ensuring that group differences are not biased by the potential effects of pharmacological treatment. We also examined the correlation between connectivity values and clinical severity scores. Based on the results obtained in children studies, we expect to find increased local connectivity in areas that comprehend DMN, fronto-parietal, and ventral attentional networks.

2. Methods

2.1. Study Design and Participants

A total of 101 participants were evaluated in this study, 39 of them were discarded because the field of view did not cover the entire brain. Thus, a total of 62 adults were selected for the present study. The ADHD group consisted of 31 adults with combined ADHD who had never received medication for their condition, and the control group was formed by 31 participants (see Table 1). We ensured both sexes were well represented in both groups (17 women in the ADHD group and 15 women in the HC group). A specialized team of psychiatrists and psychologists from Vall d'Hebron Hospital in Barcelona (Spain) evaluated the ADHD sample to ensure they all met DSM-V criteria [25] for ADHD combined subtype. ADHD symptom severity was measured by means of the ADHD Rating Scale [191, 248].

Characteristic	ADHD (N = 31) Mean (sd)	HC (N = 31) Mean (sd)	Stat (df)	p value
Age (range 19 to 52)	35.3 (9.9)	32.5 (8)	$t(60) = -1.25$	0.21
ADHD Rating Scale	32.45 (9.75)	-	-	-
Sex (number of women)	17	15	χ^2 (1) = 0.25	n.s.
Number scanned with replacement head coil	14	11	χ^2 (1) = 0.603	0.43
Framewise Displacement	0.094 (0.073)	0.065 (0.045)	$t(60) = -1.85$	0.07

Table 8: Demographic and clinical data of the ADHD and control samples. Three controls did not complete the ADHD Rating Scale. Independent sample t-tests or chi-square were used for group comparisons. None of the comparisons render significant between-group differences. Abbreviations: ADHD: Attention-Deficit and Hyperactivity Disorder; HC: Healthy Controls; sd: Standard Deviation; Stat: Statistic; df: Degrees of Freedom.

Exclusion criteria included comorbidity with other psychiatric diseases or personality disorders, which was assessed by the Structured Clinical Interview for Axis I (SCID-I)[192] and Axis II disorders [193]. Participants with substance abuse disorders (including tobacco and cannabis consumption within the last 6months), and those with an estimated WAIS-III IQ [194] lower than 80 were also excluded. The study was approved by the Hospital de Vall d'Hebron Ethics Committee, and informed consent was obtained from all participants.

2.2. MRI Acquisition

A Philips Achieva 3T scanner was used to acquire the MRI images for the present study. T1-weighted images were acquired with a fast-spoiled gradient echo (FSPGR) sequence. Acquisition parameters were as follows: repetition time (TR)=8.2 ms, echo time (TE)=3.7 ms, flip angle (FA)=88°, matrix dimensions=256×256×180, voxel size=0.94×0.94, and slice thickness=1 mm with no gap. Resting state functional magnetic resonance imaging (fMRI) data were acquired using an echo-planar imaging (EPI)-T2* sequence, which

included 116 time points, each lasting 2.655 s. Acquisition parameters were: TR=3,000 ms, TE=35 ms, FA=90°, matrix dimensions=128×128, voxel size of 1.80×1.80 mm^2, slice thickness=3.0 mm with a 1 mm gap. Participants were instructed to remain still and awake with their eyes open during the functional run.

Due to technical problems, a different radio frequency (RF) head coil (16 channels instead of 8 channels) was used for 25 out of the 62 of the participants when acquiring the MR images (see Table 1). This was considered in the analyses, although no significant differences were found in temporal contrast-to-noise ratio [249] were found between the samples of each head coil (Supplementary Table 2). Furthermore, as displayed in Supplementary Figure 2, the group differences map shows a similar trend when using the whole dataset or the eight-channel head coil sample.

2.3. MRI Processing

Preprocessing of fMRI data was performed with the software packages SPM12 (Welcome Department of Imaging Neuroscience, London, United Kingdom) and AFNI (Scientific and Statistical Computing Core, National Institute of Mental Health, Bethesda, MD). Preprocessing started by removing the first 3 volumes to allow for magnetic stabilization. Then, images were realigned to the mean image in order to correct for motion-related artifacts and despiked with the 3dDespike AFNI tool (c1=2.5, c2=4). Images were later normalized to the MNI152 stereotactic standard space for comparison purposes, and spatially smoothed with a Gaussian kernel of a full-width-half-maximum (FWHM) of 6 mm to increase the signal-to-noise ratio. Finally, all functional images were down-sampled to an isotropic 4 mm voxel size and nuisance variables (including the 6 rigid parameters obtained from the motion correction and mean white matter, mean cerebrospinal fluid and mean whole-brain signals) were regressed out to remove confounding effects. None of the participants have a mean framewise displacement (FD) over 0.5 mm, as measured by the MCFLIRT tool [198]. See Table 8 for descriptive statistics per group.

Since in-scanner motion may have a substantial impact on functional connectivity analyses [195–197], a resting-state functional connectivity quality control (RSFC-QC) was additionally plotted in order to assess the effect of motion in functional connectivity as a function of node distance. Supplementary Figure 1 suggests that in-scanner motion did not alter the relationship between functional connectivity and node distance.

2.4. Local and Distant Functional Connectivity Analysis

The local and distant functional connectivity technique is a graph-theory-based method used on resting-state fMRI data [182]. It measures the degree of connectivity of each voxel with those surrounding it (local connectivity) and with those far from it (distant connectivity). The degree of connectivity of a given voxel is computed as the number of voxels functionally connected to that target voxel.

For the present study, we first obtained a connectivity matrix for each subject, which contained the Pearson correlation coefficient of the time series of every voxel with any other voxel in the gray matter mask. This matrix was binarized by substituting correlation values higher than 0.25 by ones and the rest by zeros (following the criteria described in the original work of Sepulcre *et al.* [182]). We did not take into consideration negative correlations since the preprocessing step of global signal regression can bias the distribution of connectivity values downwards, thus potentially introducing negative correlations that were not initially present in the data [200, 201].

Local and distant functional connectivity values were calculated as the degree of functional connectivity of each voxel but with physical distance restrictions. Local connectivity maps were computed as the degree of connectivity of each voxel within its neighborhood, defined as the 28×28×28 mm^3 cube surrounding it [182]. Distant connectivity maps were computed as the degree of connectivity of a voxel with those outside its neighborhood (i.e., outside the 28×28×28 mm^3 cube).

For both functional connectivity maps, we adjusted each voxel's degree of functional connectivity according to the total number of voxels to which it could be connected. This allowed us to correct for voxel position since voxels located on the borders of the brain have part of their surrounding cube outside the brain and have less potential local connectivity and, therefore, more potential distant connectivity. The corrected distant functional connectivity value $\hat{d}_i$ was calculated using the following formula:

$$\hat{d}_i = \frac{d_i}{D_i}$$

where d_i is the distant functional connectivity value of the ith voxel and D_i is the number of voxels out of the ith voxel's cube that fall inside the brain mask, so that $\hat{d}_i$ varies from 0 to 1. Respectively, the corrected local functional connectivity value $\hat{l}_i$ was calculated using the following formula:

$$\hat{l}_i = \frac{l_i}{L_i}$$

where l_i is the local functional connectivity value of the ith voxel and L_i is the number of voxels of the ith voxel's cube that fall inside the brain mask so that $\hat{l}_i$ varies from 0 to 1.

2.5. Characterizing Local and Distant Functional Connectivity in Adults

To examine local and distant connectivity patterns in adults with and without ADHD, and visually compare the results to local and distant adult's maps obtained by Sepulcre *et al.* [182], we transformed the mean group local and distant connectivity maps to group-specific Z-score maps. This transformation was performed only for visualization purposes. Subsequent analyses used the direct local and distant connectivity values.

2.6. Statistical Analysis

Group Comparisons

Two General Linear Models were fitted, one for local and one for distant functional connectivity maps. These models included as covariates head coil, sex, individual mean FD (mean-centered to zero), and age (mean-centered to zero). For each model, specific contrasts were performed to test group differences. Analyses were performed with SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12; version 95 of September 12, 2016).

Correlations with Clinical Symptoms

Regression analyses were performed to test the associations between local and distant functional connectivity and the severity of ADHD symptoms. Two General Linear Models were fitted, one for local and one for distant functional connectivity differences, which included as regressors the score on the ADHD clinical scale (ADHD score), head coil, sex, individual mean FD (mean-centered to zero), and age (mean-centered to zero). Then, specific contrasts were performed to test the effect of ADHD score on local and distant functional connectivity.

Multiple Comparisons Correction

Statistical maps were thresholded with a p<.05 and a cluster size of at least 112 contiguous voxels, which corresponds to a cluster-wise Family Wise Error (FWE) corrected p value of .05 (p^{FWE}<.05). The FWE correction was estimated with the AFNI program 3dClustSim [203] (accessed September 11, 2018), which performs a MonteCarlo simulation based on the image size, the search volume (in this case the gray matter mask), and the spatial correlation of the image.

Functional Connectivity Differences in Areas with Altered Local Connectivity

As a post-hoc analysis, we assessed whether the alterations found in local functional connectivity co-occur with an alteration of their functional connectivity patterns. For each subject, we computed the mean blood-oxygen-level-dependent (BOLD) signal of those voxels that resulted significant in the group comparisons (p<.05 FWE corrected). Then, mean BOLD signal was correlated with that of each voxel in the brain, obtaining one connectivity map per subject. Finally, we fitted one linear model per voxel with each subject's connectivity value as dependent variable and group, sex, head coil, FD (mean-centered to zero), and age (mean-centered to zero) as independent variables. Then, specific contrasts were used to test group differences.

2.7. Cortical and Network Visualization

For visualization purposes, we calculated the percentage of voxels that pertained to each of the seven cortical large-scale resting-state functional networks described by Thomas Yeo *et al.* [19]. Surface projections of local and distant maps were performed via a Matlab in-house script that uses nearest neighbor (for the categorical classification in the seven cortical large-scale resting-state functional networks [19] or linear interpolation (for the quantitative maps) and the surface normals to project cortical voxels onto the surface. The surfaces employed were the left and right "Q1−Q6_R440.#.midthickness.164k_fs_LR.-surf.gii" of the software Connectome Workbench [204].

3. Results

3.1. Characterization

In Figure 18, maps of z-score values are projected on brain surfaces with saturation values of −2.5 (minimum) and 2.5 (maximum).

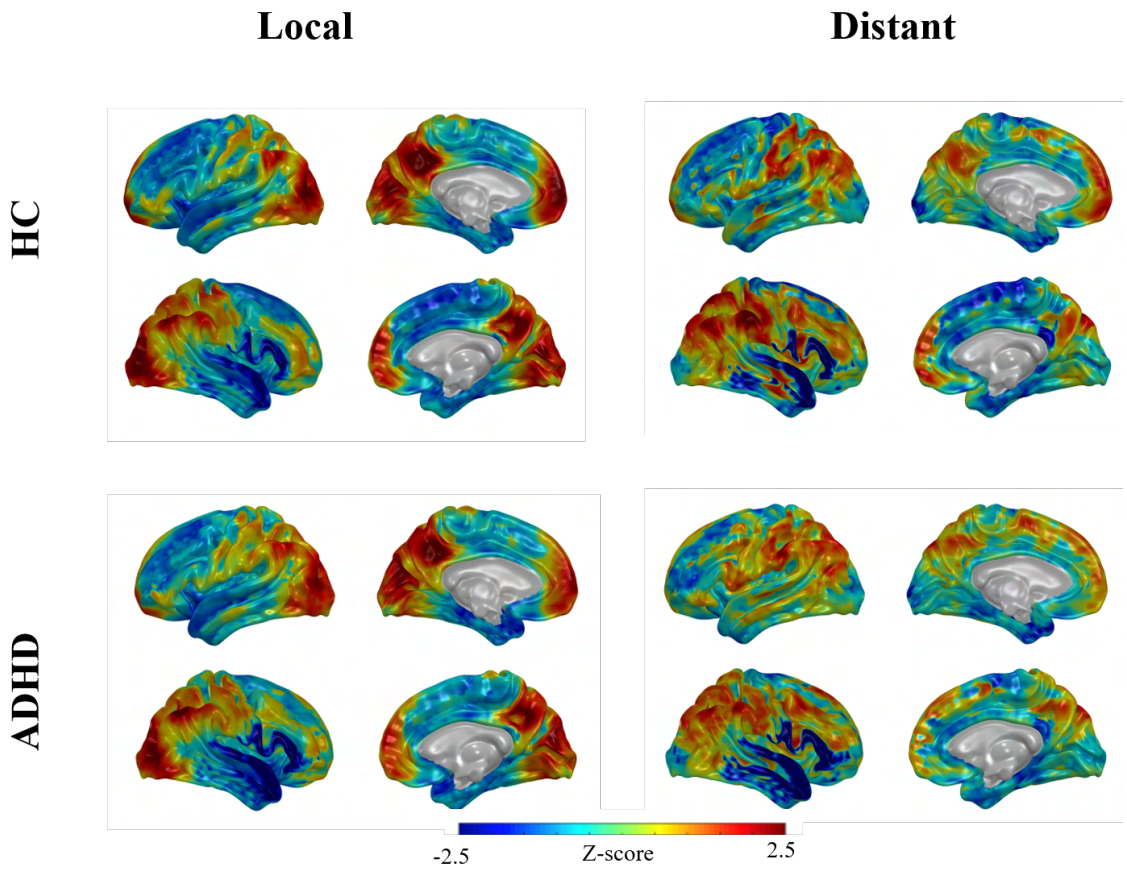


Figure 18: One-sample characterization of local and distant functional connectivity in adults with ADHD and healthy controls.

3.2. Between-group Differences

As displayed in Figure 19 and Table 9, adults with ADHD showed increased local functional connectivity in frontal regions, including the Superior Frontal Gyrus (SFG) and the dorsal Anterior Cingulate Cortex (dACC; max t=3.422) compared with controls. Regions with increased local functional connectivity mainly overlap with the frontoparietal (36%), ventral attentional (31%), and default mode (24%) networks. For further details of the percentage of overlap of the results with each network of Yeo's parcellation, see Supplementary Table 1.

Between-group Comparisons	Peak MNI Coordinates x	y	z	Number of Voxels	Highest *t* score	Cluster-level *p* value
Local functional connectivity						
ADHD >HC						
Cluster 1 (Bil. Dorsal Anterior Cingulate Cortex and R. Superior Frontal Gyrus)	11	38	40	363	3.4217	$p<0.001$
HC >ADHD						
Cluster 1 (Bil. Precuneus and Bil. Posterior Cingulate Cortex)	-8	-51	22	139	-3.8293	$p<0.02$

Table 9: Results of the local and distant functional connectivity analyses. Abbreviations: R: right; L: left; Bil: bilateral; ADHD: Attention-Deficit and Hyperactivity Disorder; HC: Healthy Controls; MNI: Montreal Neurological Institute.

Regarding the opposite contrast, adults with ADHD showed decreased local functional connectivity in an area that included part of the Precuneus and the Posterior Cingulate Cortex (now ahead PCC; max $t=-3.829$). In terms of large-scale functional networks, the regions that exhibited decreased local functional connectivity pertain mainly to the default mode network (80%) and, to a lesser extent, to the visual (8.6%) and frontoparietal (10%) networks. Finallyconcerning the distant functional connectivity analysis, no clusters survived the threshold of $p<.05$ FWE.

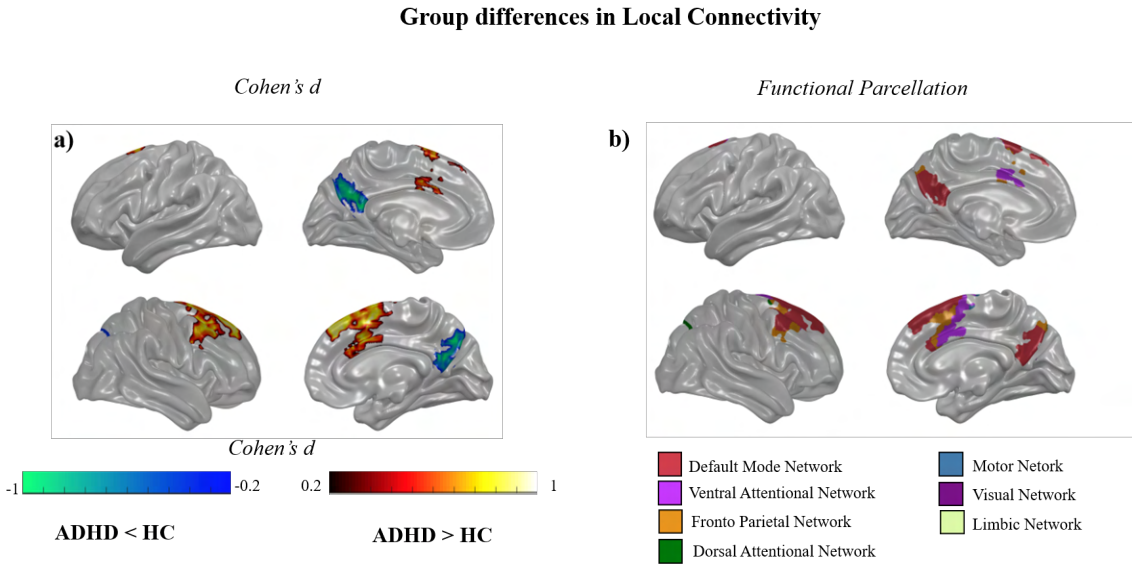


Figure 19: (a) Differences in local functional connectivity between adults with ADHD and healthy controls. (b) Group differences in local functional connectivity in terms of large-scale functional networks (Yeo et al., 2011). Each color represents a different functional network.

3.3. Symptom Severity Correlations

Figure 20 shows the results of the regression analyses between the degree of local functional connectivity and the ADHD symptom severity scale. Results revealed four clusters whose local connectivity negatively correlated significantly with the severity of ADHD symptoms. That is, higher scores on the ADHD clinical scale were associated with decreased local functional connectivity in several occipital, parietal, and frontal lobe re-

gions. Peak values of the four significant clusters were located in the medial PreFrontal Cortex mPFC (r=−.4733), the PCC (r=−.4720), the left occipital cortex (r=−.4691), and the right occipital cortex (r=−.4897; Table 10). When examined in terms of large-scale functional networks, these regions pertained mainly to the visual (44%) and default mode (41%) networks, and to a lesser extent, to the attentional (5.8%), frontoparietal (4.7%), and limbic (3.5%) networks. No significant correlations were found between ADHD score and distant functional connectivity.

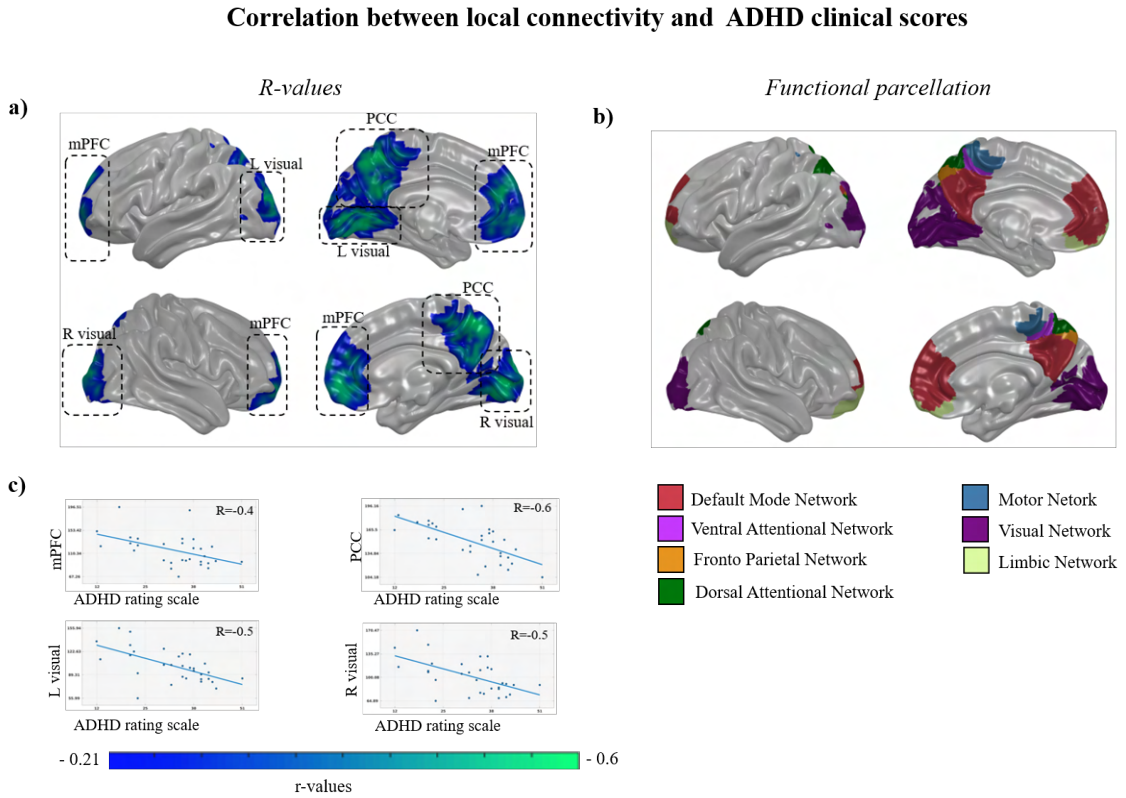


Figure 20: Correlations with clinical severity. (a) Results of the regression analyses between the degree of local functional connectivity and ADHD clinical scores. Peak-values of the four significant clusters are located in the mPFC (11, 58, −12; r=−.4733), the PCC (4, −53, 50; r=−.4720), the left Occipital Cortex (−24, −72, 0; r=−.4691), and the right Occipital Cortex (15, −84, 0; r=−.4897). (b) Results of the regression analyses in terms of large-scale functional networks [19]. Each color represents a different functional network. (c) Plots of the regression analysis using the mean local connectivity value of each cluster as dependent variable and the ADHD rating scale as independent variable. The effect of the covariables of no interest mentioned in the statistical analysis section (head coil, sex, age, and FD) was removed from local connectivity measure before plotting the regression.

3.4. Functional Connectivity Differences in Areas With Altered Local Connectivity

As a post-hoc analysis, we tested whether there were group differences in functional connectivity between the cluster in the SFG/dACC (ADHD>HC) and the rest of the brain; and between the cluster in the precuneus/PCC (HC>ADHD) the rest of the brain. As observed in Figure 21, we found greater functional connectivity in adults with ADHD

ADHD Rating Scale	Peak MNI Coordinates x	y	z	Number of Voxels	Highest r	Cluster-level p value
Local functional connectivity						
Negative associations						
Cluster 1 (L. Occipital Cortex)	-24	-72	0	169	-0.4691	$p<0.01$
Cluster 2 (Bil. medial Prefrontal Cortex)	11	58	-12	175	-0.4733	$p<0.005$
Cluster 3 (R. Occipital Cortex)	15	-84	0	133	-0.4897	$p<0.05$
Cluster 4 (Bil. Precuneus and Bil. Posterior Cingulate Cortex)	4	-53	50	232	-0.4720	$p<0.002$

Table 10: Correlation between local and distant functional connectivity measures and ADHD symptoms severity as assessed by the ADHD rating scale. Abbreviations: R,right; L,left; Bil,bilateral; ADHD: Attention-Deficit and Hyperactivity Disorder; MNI: Montreal Neurological Institute.

between the SFG/dACC cluster and the bilateral sensorimotor cortices (t=4.3013, Table 11). Regarding the precuneus/PCC cluster, adults with ADHD present a decreased level of connectivity within the precuneus (t=4.4667) and between the PCC and the bilateral medial Prefrontal Cortex (mPFC; t=4.4693), both regions pertaining to the DMN (85.91%). No other significant group differences were detected.

4. Discussion

In this study, we investigated the local and distant connectivity patterns of 31 medication-naïve adults with ADHD by cross-sectionally comparing them to 31 healthy adults. Mimicking the results observed in children with ADHD [16], we found that adults showed increased local connectivity in an area comprising part of the dACC and the SFG. In addition, adults with ADHD exhibited decreased local functional connectivity in the PCC, which is one of the nodes of the DMN. Furthermore, the lower the local functional connectivity in the PCC and other areas of the DMN, the more severe the clinical symptoms as assessed by the ADHD rating scale. As will be explained along the discussion, our results provide an integrative explanation for the three main theoretical frameworks on ADHD: the DMN interference hypothesis, the neurodevelopmental delay hypothesis, and multi-network models.

4.1. Increased Local Connectivity in the dACC/SFG

Adults with ADHD show increased local connectivity in a cluster that encompasses the dorsal part of the ACC and part of the SFG. Alterations in the dACC have been extensively reported in both children and adults with ADHD [168, 250]. The dACC is, together with the anterior insula, one of the key nodes of the Ventral Attentional Network (VAN), also known as salience network. The interplay between the VAN, the Fronto-Parietal Network (FPN), and DMN has been proposed as a critical feature in ADHD [14, 178]. Specifically, it has been suggested that ADHD symptoms related to mind wandering might result from an inability of the VAN to disengage the DMN, leading to continuous intrusions of self-referential thinking or mind wandering during executive tasks [251–253].

Connectivity Differences	Peak MNI Coordinates			Number of Voxels	Highest t	Cluster-level p value
	x	y	z			
SFG/dACC cluster (ADHD >HC)						
Cluster 1 Precentral	-6	-34	64	313	4.3013	p<0.001
PCC cluster (HC>ADHD)						
Cluster 2 Medial Prefrontal Cortex	-6	62	0	378	4.4693	p<0.001
Cluster 3 Precuneus	10	-54	8	126	4.4667	p<0.001

Table 11: Results of the seed-based functional connectivity analyses. Abbreviations: R,right; L,left; Bil,bilateral; ADHD: Attention-Deficit and Hyperactivity Disorder; MNI: Montreal Neurological Institute. Abbreviations: SFG: Superior Frontal Gyrus; dACC: dorsal Anterior Cingulate Cortex; PCC: Posterior Cingulate Cortex; ADHD: Attention-Deficit and Hyperactivity Disorder; HC: Healthy Controls; MNI: Montreal Neurological Institute.

The SFG has been less studied in the context of ADHD. This region is mainly involved in executive (dorsolateral part) and default mode (anteromedial part) processes [254]. A

recent study indicates that SFG shows decreased degree centrality in children with ADHD [255]. Moreover, it is important to note that the same cluster encompasses both the dACC and the SFG, reflecting a higher level of connectivity between VAN, FPN, and DMN. Under this paradigm, our findings dovetail with the hypothesis that in ADHD the ability of VAN to modulate the activation of FPN and DMN might be altered. Our findings also agree with the neurodevelopmental delay hypothesis. The dACC/SFG cluster lies in the boundaries separating the FPN, the VAN, and the DMN networks, thus, increased connectivity within this region might represent a sign of atypical segregation. Segregation is a developmental process through which functional connectivity between anatomically close regions is reduced or even becomes negative. Functional segregation, together with the integration between anatomically distant regions, underlies the typical developmental pattern of the large-scale functional networks [139, 226]. Reduced between-network segregation has been previously reported not only in children with ADHD [256], but also in adults with the disorder [257]. Our study reveals that the brain of patients with ADHD shows features that resemble those of a more immature brain, and suggests that, at least when the disorder has never been medicated and persists into adulthood, those features do not remit with age.

4.2. Reduced Local Connectivity in the PCC

We also found decreased local functional connectivity within the PCC in adults with ADHD. The PCC is one of the core nodes of the DMN [258–260], and one of the principal hubs of the functional whole-brain network [126]. Thus, its integration is essential during neurodevelopment for keeping the typical small-world organization of the brain and for maintaining efficient communication among different functional systems [126]. This is the first study to show that local functional connectivity within the PCC is also affected in adults with ADHD.

Neuroimaging studies have consistently reported alterations in the PCC in patients with ADHD. For instance, functional studies have found overactivation of the PCC during attentional tasks, which has been related to attentional lapses [261]. Other studies also revealed functional connectivity reductions between two of the main default mode nodes, the PCC and the mPFC [21, 167, 226], as well as functional connectivity increases between the PCC and nodes of other networks, such as the ACC and the Anterior Insula [21, 167, 168]. These studies, together with our results of decreased functional coherence within the precuneus, point toward an abnormal large-scale functional network segregation and integration that can be also explained in the context of the DMN interference hypothesis.

Furthermore, we found that the lower the degree of local connectivity within DMN regions, including the PCC, the higher the ADHD symptom severity score. This association goes in line with that found by Oldehinkel *et al.* [262] who reported that lower connectivity within the DMN was associated with the severity of inattention.

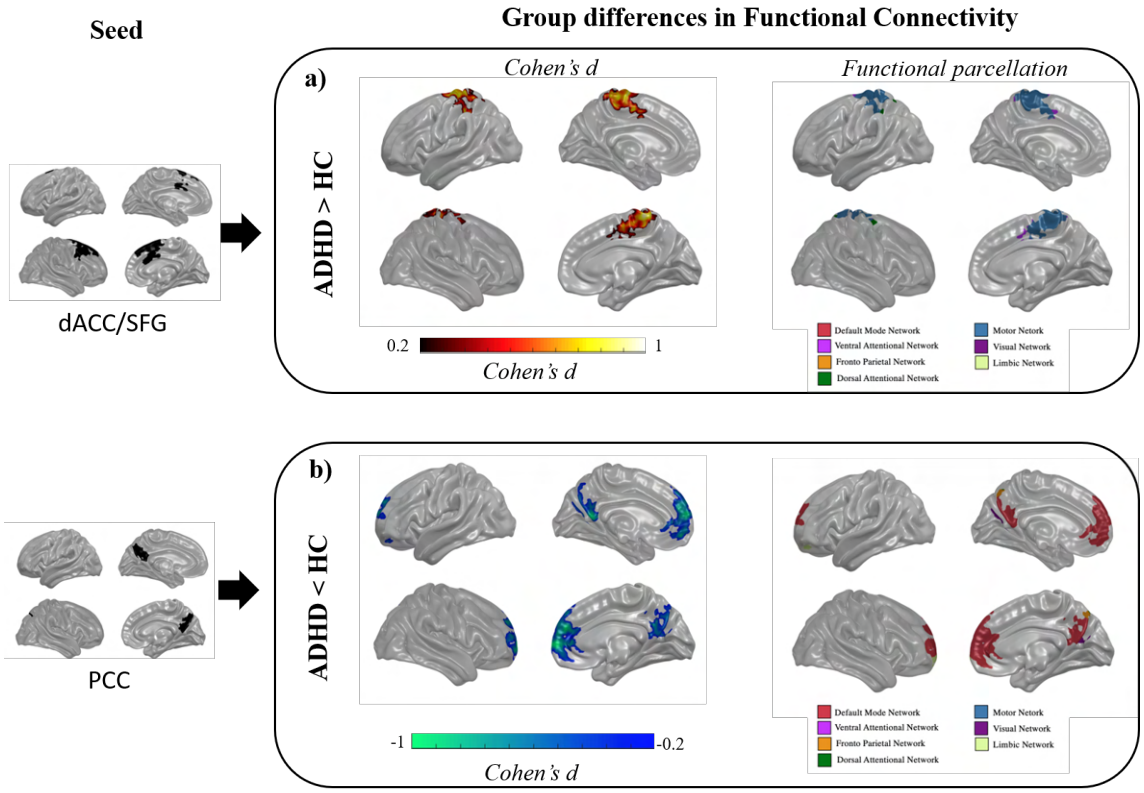


Figure 21: (a) Functional connectivity group differences taking the PCC cluster as seed. Functional connectivity group differences (PCC cluster as seed) in terms of large-scale functional networks [19]. Each color represents a different functional network. (b) Functional connectivity group differences taking the SFG/dACC cluster as seed. Functional connectivity group differences (SFG/dACC cluster as seed) in terms of large-scale functional networks [19]. Each color represents a different functional network.

4.3. Post Hoc Analyses

As post-hoc analyses, we tested whether there are group differences in functional connectivity when taking as seeds the clusters obtained from the main analyses, that is, when taking as seeds the dACC/SFG and the PCC.

On the one hand, we found that adults with ADHD showed increased functional connectivity between the dACC/SFG and the motor cortex. The dACC sends strong motor output, and has direct connections to the spinal cord and oculomotor areas, thus giving it direct control over motor action [263]. Alterations in the motor cortices have been extensively reported in ADHD using anatomical [242], diffusion tensor imaging [240, 241], task-based [243], and resting-state [178] fMRI data. According to previous data they might be related mainly to motor symptoms [262, 264] although this statement cannot be directly extracted from our data.

On the other hand, when taking the PCC as a seed we found decreased functional connectivity between that cluster and the mPFC in patients with ADHD. As previously stated, the mPFC and the PCC are the two principal hubs of the DMN, and thus, show a high level of functional connectivity in neurotypical populations [165]. Our results are

consistent with previous reports that show reduced between-region integration within the DMN [21, 167, 265]. In fact, they extend the previous literature by suggesting that the decreased inter-region connectivity between the PCC and the mPFC might be related to decreased integration, or decreased local connectivity, within the PCC. According to that, the reduced local connectivity within the PCC offers a parsimonious explanation of previous reports indicating less integration within the DMN, as well as poor communication between the DMN and the rest of the brain networks. It would be interesting that future studies test whether atypical within and between network connectivity can be explained in terms of atypical local connectivity, as a similar overlap of within and between regions connectivity has also been observed in many other psychiatric disorders [266–269].

4.4. Relation With the Results in Children

To date, this is the first study that explores local and distant functional connectivity in adults with ADHD. Our results are similar to those obtained in children [16]. Specifically, both samples exhibited greater local connectivity in areas of the SFG and the dACC. This suggests a persistent lack of segregation between DMN, VAN, and FPN across development in those areas. However, children with ADHD did not show decreased local connectivity in the PCC. The PCC is thought to be one of the most important regions in ADHD etiology [169, 187] and its activation and connectivity normalizes with methylphenidate medication. Thus, the different results in children and adults with ADHD concerning the PCC could be explained by the medication condition of the children, as some of them were medicated/ has been previously medicated [211, 270, 271]. While the child sample contained both medicated and medication-naïve children, all the adults have never received medication. However, all these comparisons must be taken with care, since we are making inferences in developmental trajectories from cross-sectional data.

5. Limitations and Conclusions

Limitations

One of the main limitations of this study is the relatively small sample size. Even though it is challenging to recruit medication-naïve adults with ADHD, the fact is that reduced sample sizes imply low power of statistical analyses. Another limitation of this study is the cross-sectional nature of the data that prevent us from directly testing the neurodevelopmental delay hypothesis. Another limitation is the usage of different head coils for some of the participants. Although we have controlled the effect of the head coil in the statistical analysis, it is difficult to know exactly its effects on results.

Conclusions

In summary, we compared the local and distant functional connectivity patterns between adults with ADHD and healthy adults. We found that adults with ADHD show increased local connectivity within the dACC and the SFG, and decreased local functional connectivity within the PCC. We also found that PCC's local connectivity is correlated with clinical symptomatology, and that this region presents a decreased level of functional connectivity with the mPFC. These findings reflect a level of integration and segregation proper of a more immature brain, and that affects the regions and networks relevant for the DMN interference hypothesis. Moreover, secondary analyses also show alterations of sensory networks as well, specifically visual and sensorimotor cortices, highlighting the importance of the interplay between basic sensory-motor and higher-order cognitive circuits.

Funding

This work was supported by Ministerio de Ciencia, Innovación y Universidades project RTI2018-093952-B-100 and by Instituto de Salud Carlos III projects CPII21/00016 and PI17/00064, and co-funded by European Regional Development Fund (ERDF), “A way of making Europe.” MMG was funded by Ministerio de Ciencia, Innovación y Universidades, Instituto de Salud Carlos III, Predoctorales de Formación en Investigación en Salud (PFIS) (contract FI18/00255) and a predoctoral Fulbright grant and SC was funded by a Miguel Servet Type II research contract (CPII21/00016). MMG and SC were co-funded by European Social Fund “Investing in your future.” The project leading to these results has received funding from “la Caixa” Foundation under the project code LCF/PR/HR19/52160001, from the European Research Council (ERC) under the “European Union’s Horizon 2020" research and innovation programme (grant agreement No 883069), and from the Centro Nacional de Investigaciones Cardiovasculares (CNIC). The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-050).

DISCUSSION

The present dissertation aims to determine whether there is an alteration of the global brain organization in people with ADHD that may underlie the features that characterize the different neurobiological models of the disorder. For that, we will apply two different graph-theory methods based on systems science to the resting-state functional Magnetic Resonance Imaging data of adults and children with ADHD.

The first of the methods is called Stepwise Functional Connectivity (SFC) and evaluates the multilevel information processing streams in terms of topological distance. Thus, it provides information about the consolidation of sensory regions in terms of direct connections between them and the integration of information into regions related to high-order cognitive functions. This method was previously applied to children with ADHD [178] and *Study 1* extends it by applying it to medication-naïve adults with the disorder. *Study 2* and *Study 3* apply a technique called Local and Distant Functional Connectivity (LFC and DFC), which relates topological and physical distances and gives information about how each voxel is connected with those spatially around them and those far away. *Study 2* explores LFC and DFC in children with ADHD using the same sample used in Carmona *et al.* [178] and *Study 3* applies the same method to the sample of adults used in *Study 1* (with the inclusion of 9 new participants, as described in the Section 2.1 of *Study 3*). The consistency of the samples allows us to directly relate the results obtained from the different methods for a more complete interpretation of them. Besides, the combination of the information provided by these two methods is sensitive to be interpreted under the main neurobiological frameworks that explain ADHD, namely, the dual-pathway model, the maturational lag hypothesis, the DMN interference hypothesis, and multi-network models. So since the results of the different studies are already discussed in their respective discussion sections, this general discussion will focus more on the relationship between them.

As summarized in Figure 22, our results consist of a set of alterations distributed throughout the brain that affect most of the FNs, some as increases and some as decreases in the functional network properties. These widespread results suggest a differential configuration of the whole brain network affecting how the information is transmitted globally instead of specific deficits in localized areas. This, however, does not mean that the abundant structural and functional abnormalities found in concrete regions of the brain of people with ADHD are false positive results, but that they represent different parts of the same alteration affecting the whole brain network [8, 9]. Interestingly, no significant results were found in DFC in *Study 2* nor *Study 3*. This can be due to a real lack of changes

in distant functional connectivity (which is highly unlikely if we review the previous literature), a compensation between increases and decreases in long-range connections since DFC is a global measure, or that the number of connections that change is small with respect to the total number of distant connections.

	Sample	Group Comparisons	Symptoms Correlation
Stepwise Functional Connectivity	**Children** Carmona et al., 2015	• Greater SFC in SN at low steps. • Greater SFC in VN at low and high steps. • Greater SFC in a DMN at high steps. • Reduced SFC in VAN at low and medium steps. • Reduced SFC in FPN at medium and high steps.	———
	Adults Study 1	• Greater SFC in VN at medium to high steps. • Reduced SFC in DMN at medium steps.	• Greater SFC in SN at medium to high steps is related with greater severity in adults with ADHD. •Lower SFC in DMN at medium to high steps is related to greater severity in adults with ADHD.
Local Functional Connectivity	**Children** Study 2	• Greater Local Connectivity in a region where FPN, VAN and DMN converge. • Greater Local Connectivity in a VAN region.	• Greater Local Connectivity in SN is related with greater severity in both children with ADHD and ND children.
	Adults Study 3	• Greater Local Connectivity in a region where FPN, VAN and DMN converge. • Reduced Local Connectivity in a DMN region.	• Lower Local Connectivity in DMN is related with greater severity in adults with ADHD. • Lower Local Connectivity in VN is related with greater severity in adults with ADHD.

Figure 22: Summary of the main results of the four scientific articles that apply SFC, LFC and DFC to children and addults with ADHD.

Study 1 is the first to explore the SFC patterns of medication-naïve adults with ADHD, even though this method was previously applied to children with the disease [178]. In the case of the VN, we found that adults with ADHD show greater SFC at short to long link-step distances, which could intuitively be related to the general hyperconnectivity of the visual cortex previously described in ADHD [135, 175, 177]. However, this is unlikely since Study 3 did not find any LFC increases in the visual cortex using the same sample and lower LFC in that area predicted higher severity of ADHD symptoms. So it is probable that the alterations that we and Carmona *et al.* [178] and colleagues found in the VN are related to a more associative role in the global functional network, which supports previous findings of increased nodal efficiency of the visual cortex of children with ADHD [272]. Regarding the DMN, we found an opposite pattern of differences in this study, that is, that adults with ADHD showed decreased SFC at medium link-step distance (5 steps) in the mPFC. Furthermore, the lower SFC at low to high link-step distances in the two core regions of the DMN (PCC and mPFC), the higher their symptom score. Areas of the DMN are some of the most consistently reported to be altered in ADHD, especially (but

not exclusively) in studies involving FC [169, 187, 273]. In our case, the results in SFC overlap with those of LFC by which there is a decreased level of connectivity in the PCC, as will be discussed when interpreting *Study 3*.

Study 2 was the first to explore LFC and DFC patterns in the ADHD population, specifically in children with ADHD (with the same sample used in Carmona *et al.* [178]). The results show an increase in LFC in two clusters lying in the boundaries between the DMN, the VAN, and the FPN, which suggests a lack of segregation between these networks that had already been described in ADHD [154]. The interplay between them has been suggested as a critical feature in multiple explanations of ADHD, from the DMN interference hypothesis [13] to multi-network models that also include the VAN regulating the DMN-FPN interaction [14, 170]. Apart from the involvement mentioned above of DMN in ADHD, FPN is related to some of ADHD's core symptoms, such as sustained attention or response inhibition [19, 274]. Additionally, a different age trajectory of the SN was found where LFC tended to decrease with age in ND children while in children with ADHD remained stable or even increased. Using the same sample, Carmona *et al.* [178] found greater SFC at direct distance in the SN, which reveals the high importance of this area in the understanding of the disease as it has been suggested by structural, diffusion, and functional studies [240–243](An et al., 2013). Moreover, LFC in this network predicted symptom severity in both children with ADHD and ND children pointing to a continuous relation between these variables in the global population.

Finally, *Study 3* examined the same LFC and DFC metrics in medication-naive adults with ADHD. We found increased LFC in a cluster that overlaps with the one found in children (Figure 23) and encompasses the DMN, the VAN, and the FPN. A post-hoc analysis revealed that this brain area also presented greater FC with the motor cortex. This is especially relevant because the aforementioned cluster includes the dorsal Anterior Cingulate Cortex (dACC), a VAN region tightly related to motor functions [275]. Conversely, adults with ADHD showed decreased LFC in an area in the mPFC, which is one of the main core nodes of the DMN, and this area also exhibited lower FC with the PCC (the other core component of the DMN)[165] in post-hoc analysis. This points to a lack of integration within the mPFC, which could also be responsible for the lack of integration between the two components of the DMN. In other words, if the voxels within one node have different behaviors, there are fewer potential similar voxels to the ones of the mPFC. The relation between these results and the ones in *Study 1* lies in the fact that in a densely connected subnetwork, multiple pathways reach each of its nodes, even from the outside. This happens because of combinatory properties of the graph since once a path has reached a node of the subnetwork, there are a great number of ways to reach any of its other nodes. Moreover, both SFC and LFC levels in these two regions predict ADHD symptoms negatively, that is, the lower the metric, the higher the severity.

To summarize, we found four main alterations in ADHD using SFC and LFC: a more associative role of the VN, increased integration of the SN, decreased integration within

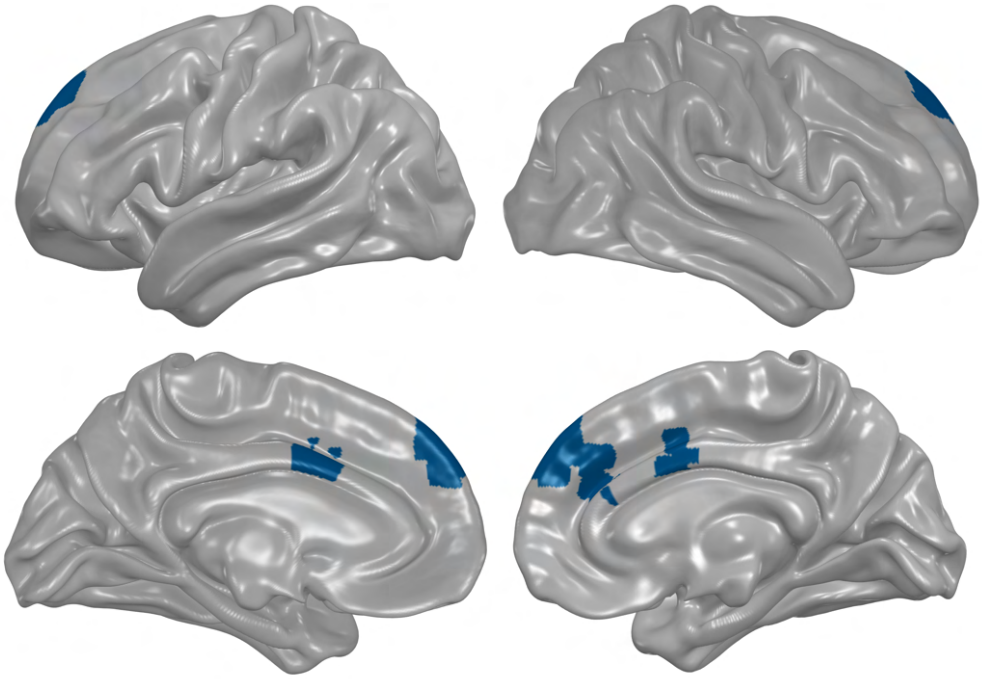


Figure 23: Clusters where LFC is increased in both children and adults with ADHD.

and between nodes of the DMN, and decreased segregation between the DMN, the FPN, and the VAN. The following section will describe the similarities and dissimilarities between the SFC and LFC patterns of adults and children with ADHD and the possible source of these differences. The final section of the discussion will explain how the alterations we found can be contextualized in terms of the main neurobiological models of ADHD, suggesting that all of them can be explained in terms of alterations of the properties of the whole brain network.

Relationship between adults and children

The results in adults partially resemble those of children with ADHD. In both samples, increased SFC has been found in the VN but, while in adults we found them from short to long functional distances (3,5 and 7 steps), Carmona *et al.* [178] also found increased SFC at direct functional distance in children (1 step)[178]. These results highlight that the visual system is altered in both children and adults with ADHD, and structural abnormalities have indeed been found in the visual cortex of both populations [276, 277]. Moreover, a 33-year follow-up study related the persistence of ADHD diagnosis into adulthood with decreased cortical thickness in the visual cortex [278].

Another sensory network that we consistently found to be altered is the SN. There

is a general pattern of increased integration within the SN in children and adults with ADHD and a positive relationship between this integration and symptomatology. Again, one study found cortical morphology alterations in adults and adolescents with ADHD [213]. Furthermore, the FC between the sensorimotor cortex and associative areas during a go/no-go task (a task that measures control inhibition) was equal in healthy controls than in ADHD remitters but altered in people with persistent ADHD [279], which suggests an essential role of the SN in the remission of ADHD when reaching adulthood.

One of the most striking findings of this dissertation is the overlap in LFC increases in the dACC/SFG of the children and adult samples, which is displayed in Figure 11. The magnitude of the FC between the dACC and the PCC (which in healthy population is negative) is decreased in both children and adults with ADHD [155, 167], and this feature was proposed as a core locus of dysfunction in ADHD [167]. However, we found that local segregation between the DMN and the VAN in areas around the dACC is reduced, but whether this is related to its altered FC with the PCC or not needs to be further investigated.

The main discrepancies between children and adult samples lie in regions typically associated with the DMN. Carmona *et al.* [178] found increased SFC at long functional distance, while in adults we found a decrease in SFC at medium functional distance. Moreover, the region of the DMN showing this (almost) opposite pattern of SFC is the same: the mPFC. In LFC, no differences were found in any DMN area in children, but the LFC of the mPFC was reduced in adults. The important role of the DMN in ADHD has been consistently reported [169, 273], and the difference found could be due to the fact that some of the children were medicated [211, 270, 271] while adults were not.

All in all, we found convergences in most of the areas affected in children and adults with ADHD. Most of the discrepancies occur in SFC where, apart from the opposite pattern in the DMN, we did not find any alterations in areas of the VAN or the FPN, while Carmona et al. did. Again, this could be due to the effect of medication, or it could also reflect different subtypes of ADHD. Future remitters and prevalent ones can pertain to the children sample, and in the adult sample, we could have a group of the hypothesized late-onset ADHD [30]. But without knowing the age of onset of the adults, it is impossible to elucidate it. Finally, the interpretation of this section, although crucial for understanding a neurodevelopmental disease, must be taken with care since we are making inferences about longitudinal trajectories with cross-sectional data.

Integrating the different neurobiological models of ADHD

In this section, I will interpret each of the main results of the dissertation in terms of the four neurobiological models of ADHD to test whether they can be considered incomplete views of a global brain alteration. For that, I will relate each of the main results with previous literature, focusing on the models applicable to them. For example, alterations

in sensory regions cannot be related to the DMN interference hypothesis. Multinetwork models, on the other hand, even if they are applicable by default because we found alterations in multiple networks, will only be mentioned if a specific model coincides with our results.

As pointed out, alterations in the visual cortex may reflect a more associative role in this area. This means that its functional connectivity with areas related to other functions is increased and, thus, that it is less segregated from them. In Gu *et al.* [280], the authors studied the segregation and integration patterns of different networks during brain maturation, showing that both VN's integration and segregation increased across development [280]. So a mature VN is, in their own words, a "cohesive provincial" network in that it has high within-network connectivity but low connectivity with other networks [280–282]. Our findings are thus coherent with a more immature state of the VN but in terms of its relationship with other networks and, maybe, its role in the global brain network. This supports previous findings of delayed cortical thickness trajectories in the VN of people with ADHD [144], highlighting the relevance of multimodal studies that explore the relationship between these two brain features.

In the case of the SN, we found that greater integration within the network predicts higher severity in ADHD scores. The developmental pattern of the FC of this subnetwork is mostly plain, that is, the SN presents a high level of within-network FC from at least two weeks of age, and it remains more or less like that for the next years [280, 283]. Thus, our findings point more to an aberrant configuration of the SN than to delayed cortical maturation of this region, as supported by the differential age trajectories we found in children with ADHD. Moreover, this goes in line with previous findings that pointed to the motor cortex as the exception of the maturational lag hypothesis, showing a faster development in ADHD [144].

The decreased DMN integration that we found can be explained under both the DMN interference hypothesis and as a maturational lag. The architecture of the DMN suffers great change from being a group of sparsely connected regions in young children to a densely integrated component of the brain in adulthood [209]. Moreover, during childhood and adolescence the integration is also related to age, with greater within-network integration in older children and adolescents than in young ones [284–286]. Our results can thus be interpreted as a sign of immaturity, but since we also found decreased integration in adults with ADHD, it is unlikely that this lag catches up with age. Reduced integration within the DMN can be due to a more task-positive behavior of some of its regions, which would be related to the multiple studies reporting decreased segregation between the DMN and areas of task-positive networks [155, 167]. This relation comes from the fact that if part of the DMN has a more task-positive behavior, but other parts are still task-negative, their connectivity will be reduced, and thus, we will be facing an alteration of local integration. Since the local specialization in different FN is a process that occurs during development [139, 196, 229], the ubiquitous alterations of the DMN in ADHD could simultaneously support two of the strongest models that explain the disease.

We found indeed decreased segregation at a local level between the DMN and task-positive networks. The local decreased segregation between DMN, VAN, and FPN in the dACC can be interpreted as one of the main alterations of the DMN interference hypothesis [155, 167] and the triple-network model, which is a multinetwork model [14]. Moreover, the local-to-distributed pattern of development of FC [139] and the lack of segregation between proximate areas that we found are directly linked with the maturational lag. This lack of segregation between regions of the DMN-FPN-VAN triplet has previously been described as a sign of immaturity in people with ADHD [21, 154].

The only model that evades our results is the dual-pathway model. This is one of the oldest models of ADHD and characterized the disease as a dysfunction of two localized corticostriatal streams in the brain [11, 12]. We did not find any significant alterations in subcortical structures, but LFC will not probably work in small volumetric regions like the subcortical structures as well as in the cortex, and SF does not even analyze the basal forebrain. However, the amount of previous evidence of alterations in areas out of the ones involved in this model has proven it insufficient [187]. However, even if we did not find alterations in areas directly related to this model, our measures are based on the relation with other parts of the brain and, thus, some of the alterations we find may be related to the "hot" and "cool" corticostriatal pathways. For instance, the DMN interference hypothesis is linked to subcortical structures since they play an important role in the activation and suppression of this FN [287]. Besides, the two methods we used measure some properties of the whole functional network, but maybe the alterations in these circuits concern different network properties.

Altogether, we found alterations that are highly compatible with the maturational lag hypothesis regarding a lack of segregation between the VN and other FNs, a decreased integration within the DMN, and a lack of segregation between DMN, VAN, and FPN. The DMN interference hypothesis was supported by the decreased integration of the DMN and the increased segregation between the DMN, VAN, and FPN. Finally, this lack of segregation reinforces the triple network model, but wider multinetwork models are required to explain the alterations in sensory systems. However, we propose to analyze the brain as a whole brain network instead of a group of segregated systems (as multinetwork models typically do), even though this segregation may help relate alterations to cognitive functions.

Concluding remarks

ADHD is one of the most prevalent disorders during childhood and one of the hobgoblins of mental health these days. Public imagination has situated ADHD as a highly overdiagnosed disorder and, in extreme cases, as a fiction created by pharmaceutical enterprises to sell drugs. Besides, the capitalist and consumerist western model of society propels the cognitive structure of ADHD among its citizens. On the one hand, the constant availabil-

ity of services and products difficults the process by which the "cool" processing pathway suppresses the "hot" one, so the immediate reward is more prone to surpass a delayed one. On the other hand, there is a continuous bombardment of highly relevant stimuli to attract attention to products and services, and by habituation this can make us less reactive to less intense stimuli. This collective change in cognitive processing patterns can alter some mental properties, at least as we have defined them in tests.

As an example of the aforementioned cognitive patterns, we can take a look at music (the examples can be found in the QRs below). The pinnacle of mainstream music now can be the Spanish singer Rosalía, and I think her last album and specially the song CUUUUUuuuuuute is a perfect example of some ADHD features in society. We find short songs (2 or 3 mins each) with highly relevant stimuli in both terms of music and lyrics, and even though the songs are short, there are abrupt changes in them with a whole different stimulus set. By contrast, I have chosen music from different temporal and cultural locations, characterized by longer duration and lower relevance stimuli, thus requiring sustained attention and more cognitive effort to enjoy the whole songs. As an old example, I have chosen the Saxophone Concerto of Alexander Glazunov and, as a contemporary one, All Melody from Nils Frahm, both using repeating patterns with variations on and over them.

However, this is not about music quality (which is entirely out of the scope of this dissertation) but about noting how social changes can affect what we consider symptoms of mental disorders. One curious anecdote is that two out of three people I told this past month about my dissertation were self-diagnosed with ADHD. Since epidemiology does not support this numbers, the self-perception of ADHD's symptoms are more probably related to a transition in cognitive abilities than a real diagnosis. So to really understand ADHD, we must consider social changes and constantly revisit how we measure its symptoms and how they are distributed in the whole population. And it is crucial that we understand brain function so we define the neurobiological bases of ADHD, which will improve diagnosis, and treatment and, thus, improve people's life quality.

CUUUUuuuuuute
Rosalía

Concerto for Saxophone, Op. 109
Alexander Glazunov

All Melody
Nils Frahm

CONCLUSIONS AND FUTURE DIRECTIONS

The present dissertation aims to determine whether there is an alteration of the global brain organization in people with ADHD that may underlie the features that characterize the different neurobiological models of the disorder. For that, we have applied two different graph-theory methods based on systems science to the resting-state functional Magnetic Resonance Imaging data of adults and children with ADHD.

Study 1 was the first to analyze the Stepwise Functional Connectivity patterns of medication-naïve adults with ADHD, a method that was previously applied to children with the same disease. We found alterations affecting multiple brain subsystems: a lack of segregation between the VN, a lack of integration within the DMN, and increased integration within the SN. *Study 2* was the first to analyze the Local and Distant Functional Connectivity patterns of children with ADHD. Again, we found various alterations in the brain functional network, namely, a lack of segregation between the DMN and task-positive networks and excessive integration within the SN that predicts ADHD as a trait in the whole sample. Finally, *Study 3* explored the same Local and Distant Functional Connectivity patterns but to medication-naïve adults with ADHD. We found alterations compatible with both previous studies: a lack of integration within the DMN and decreased segregation between the DMN and task-positive networks.

Each of the currently available neurobiological models that characterize ADHD is able to explain part of the results that we found, which suggests that all of them are different views of the same global alteration of the functional brain architecture. This alteration may affect information processing, highlighting the need to study the pathological brain globally rather than looking for localized alterations that function independently.

However, studying the global brain network is conceptually challenging, and more advanced techniques are needed to understand complex systems like the brain. Multilayer networks is a promising technique that can analyze multimodal information, thus exploring the relationship between structural alterations and functional connectivity is on the roadmap of my career as a postdoc. We also aim to explore dynamic connectivity, a technique that provides a more accurate approximation of neural coupling and its variations over time. Finally, I believe it is necessary to study the disorder based on the conception of ADHD as a continuous trait represented in the population and not as a dichotomous label.

BIBLIOGRAPHY

[1] S. Carmona *et al.*, "Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes," *Human Brain Mapping*, vol. 40, no. 7, pp. 2143–2152, May 2019. DOI: 10.1002/HBM.24513.

[2] K. Martínez *et al.*, "Sensory-to-Cognitive Systems Integration Is Associated With Clinical Severity in Autism Spectrum Disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 59, no. 3, pp. 422–433, Mar. 2020. DOI: 10.1016/j.jaac.2019.05.033. [Online]. Available: http://www.jaacap.org/article/S0890856719304459/fulltext.

[3] M. Martínez-García *et al.*, "Do Pregnancy-Induced Brain Changes Reverse? The Brain of a Mother Six Years after Parturition," *Brain Sciences 2021, Vol. 11, Page 168*, vol. 11, no. 2, p. 168, Jan. 2021. DOI: 10.3390/BRAINSCI11020168. [Online]. Available: https://www.mdpi.com/2076-3425/11/2/168/htm%20https://www.mdpi.com/2076-3425/11/2/168.

[4] F. J. Navas-Sánchez *et al.*, "Thalamic atrophy in patients with pure hereditary spastic paraplegia type 4," *Journal of Neurology 2021 268:7*, vol. 268, no. 7, pp. 2429–2440, Jan. 2021. DOI: 10.1007/S00415-020-10387-4. [Online]. Available: https://link.springer.com/article/10.1007/s00415-020-10387-4.

[5] F. J. Navas-Sánchez *et al.*, "Corticospinal tract and motor cortex degeneration in pure hereditary spastic paraparesis type 4 (SPG4)," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 23, no. 1-2, pp. 25–34, Jan. 2022. DOI: 10.1080/21678421.2021.1962353. [Online]. Available: https://www.tandfonline.com/doi/full/10.1080/21678421.2021.1962353.

[6] F. J. Navas-Sánchez *et al.*, "Tract-specific damage at spinal cord level in pure hereditary spastic paraplegia type 4: a diffusion tensor imaging study," *Journal of Neurology 2021 269:6*, vol. 269, no. 6, pp. 3189–3203, Jan. 2022. DOI: 10.1007/S00415-021-10933-8. [Online]. Available: https://link.springer.com/article/10.1007/s00415-021-10933-8.

[7] A. Fernández-Pena *et al.*, "ABLE: Automated Brain Lines Extraction Based on Laplacian Surface Collapse," *Neuroinformatics 2022*, pp. 1–18, Aug. 2022. DOI: 10.1007/S12021-022-09601-7. [Online]. Available: https://link.springer.com/article/10.1007/s12021-022-09601-7.

[8] F. Samea *et al.*, *Brain alterations in children/adolescents with ADHD revisited: A neuroimaging meta-analysis of 96 structural and functional studies*, May 2019. DOI: 10.1016/j.neubiorev.2019.02.011.

[9] H. Hulshoff Pol and E. Bullmore, "Neural networks in psychiatry," *European Neuropsychopharmacology*, vol. 23, no. 1, pp. 1–6, Jan. 2013. DOI: 10.1016/j.euroneuro.2012.12.004.

[10] E. El-Sayed, J. O. Larsson, H. E. Persson, P. J. Santosh, and P. A. Rydelius, *"Maturational lag" hypothesis of attention deficit hyperactivity disorder: An update*, 2003. DOI: 10.1080/08035250310002777.

[11] E. J. S. Sonuga-Barke, "Psychological heterogeneity in AD/HD-a dual pathway model of behaviour and cognition," Tech. Rep., 2002, pp. 29–36. [Online]. Available: www.elsevier.com/locate/bbr.

[12] E. J. Sonuga-Barke, "The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics," in *Neuroscience and Biobehavioral Reviews*, vol. 27, Elsevier Ltd, 2003, pp. 593–604. DOI: 10.1016/j.neubiorev.2003.08.005.

[13] E. J. Sonuga-Barke and F. X. Castellanos, "Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis," *Neuroscience and Biobehavioral Reviews*, vol. 31, no. 7, pp. 977–986, 2007. DOI: 10.1016/j.neubiorev.2007.02.005.

[14] V. Menon, "Large-scale brain networks and psychopathology: A unifying triple network model," *Trends in Cognitive Sciences*, vol. 15, no. 10, pp. 483–506, 2011. DOI: 10.1016/j.tics.2011.08.003. [Online]. Available: http://dx.doi.org/10.1016/j.tics.2011.08.003.

[15] F. X. Castellanos, E. J. Sonuga-Barke, M. P. Milham, and R. Tannock, "Characterizing cognition in ADHD: Beyond executive dysfunction," *Trends in Cognitive Sciences*, vol. 10, no. 3, pp. 117–123, Mar. 2006. DOI: 10.1016/j.tics.2006.01.011. [Online]. Available: http://www.cell.com/article/S1364661306000283/fulltext%20http://www.cell.com/article/S1364661306000283/abstract%20https://www.cell.com/trends/cognitive-sciences/abstract/S1364-6613(06)00028-3.

[16] L. Marcos-Vidal *et al.*, "Local functional connectivity suggests functional immaturity in children with attention-deficit/hyperactivity disorder," *Human Brain Mapping*, 2018. DOI: 10.1002/hbm.24013.

[17] C. Pretus *et al.*, "Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder," *Human Brain Mapping*, vol. 40, no. 16, pp. 4645–4656, Nov. 2019. DOI: 10.1002/HBM.24727. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1002/hbm.24727%20https://onlinelibrary.wiley.

com/doi/abs/10.1002/hbm.24727%20https://onlinelibrary.wiley.com/doi/10.1002/hbm.24727.

[18] L. Marcos-Vidal *et al.*, "Local Functional Connectivity as a Parsimonious Explanation of the Main Frameworks for ADHD in Medication-Naïve Adults," *Journal of Attention Disorders*, p. 108 705 472 211 016, Jun. 2022. DOI: 10.1177/10870547221101646. [Online]. Available: http://journals.sagepub.com/doi/10.1177/10870547221101646.

[19] B. T. Thomas Yeo *et al.*, "The organization of the human cerebral cortex estimated by intrinsic functional connectivity," *Journal of Neurophysiology*, 2011. DOI: 10.1152/jn.00338.2011.

[20] F. Fan *et al.*, "Development of the default-mode network during childhood and adolescence: A longitudinal resting-state fMRI study," *NeuroImage*, vol. 226, Feb. 2021. DOI: 10.1016/j.neuroimage.2020.117581.

[21] C. Sripada, D. Kessler, Y. Fang, R. C. Welsh, K. Prem Kumar, and M. Angstadt, "Disrupted network architecture of the resting brain in attention-deficit/hyperactivity disorder," *Human Brain Mapping*, 2014. DOI: 10.1002/hbm.22504.

[22] A. M. Clare Kelly, L. Q. Uddin, B. B. Biswal, F. X. Castellanos, and M. P. Milham, "Competition between functional brain networks mediates behavioral variability," *NeuroImage*, 2008. DOI: 10.1016/j.neuroimage.2007.08.008.

[23] J. Sepulcre, M. R. Sabuncu, T. B. Yeo, H. Liu, and K. A. Johnson, "Stepwise Connectivity of the Modal Cortex Reveals the Multimodal Organization of the Human Brain," *Journal of Neuroscience*, vol. 32, no. 31, pp. 10 649–10 661, Aug. 2012. DOI: 10.1523/JNEUROSCI.0759-12.2012. [Online]. Available: https://www.jneurosci.org/content/32/31/10649%20https://www.jneurosci.org/content/32/31/10649.abstract.

[24] J. Sepulcre, "Integration of visual and motor functional streams in the human brain," *Neuroscience Letters*, vol. 567, pp. 68–73, May 2014. DOI: 10.1016/J.NEULET.2014.03.050.

[25] APA, *American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (5th ed.)* 2013.

[26] S. V. Faraone *et al.*, "Diagnosing adult attention deficit hyperactivity disorder: Are late onset and subthreshold diagnoses valid?" *American Journal of Psychiatry*, vol. 163, no. 10, pp. 1720–1729, 2006. DOI: 10.1176/AJP.2006.163.10.1720/ASSET/IMAGES/LARGE/Q915F0.JPEG.

[27] G. Polanczyk, M. Silva de Lima, B. Lessa Horta, J. Biederman, and L. Augusto Rohde, "Article The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis," Tech. Rep., 2007.

[28] G. V. Polanczyk, E. G. Willcutt, G. A. Salum, C. Kieling, and L. A. Rohde, "ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis," *International Journal of Epidemiology*, vol. 43, no. 2, pp. 434–442, 2014. DOI: 10.1093/ije/dyt261.

[29] V. Simon, P. Czobor, S. Bálint, Á. Mészáros, and I. Bitter, *Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis*, Mar. 2009. DOI: 10.1192/bjp.bp.107.048827.

[30] P. Asherson and J. Agnew-Blais, *Annual Research Review: Does late-onset attention-deficit/hyperactivity disorder exist?* Apr. 2019. DOI: 10.1111/jcpp.13020.

[31] A. J. Kotimaa *et al.*, "Maternal smoking and hyperactivity in 8-year-old children," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 42, no. 7, pp. 826–833, 2003. DOI: 10.1097/01.CHI.0000046866.56865.A2.

[32] V. S. Knopik *et al.*, "Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: A female twin study," *Psychological Medicine*, vol. 35, no. 5, pp. 625–635, May 2005. DOI: 10.1017/S0033291704004155.

[33] J. T. Nigg and N. Breslau, "Prenatal smoking exposure, low birth weight, and disruptive behavior disorders," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 46, no. 3, pp. 362–369, Mar. 2007. DOI: 10.1097/01.chi.0000246054.76167.44.

[34] Q. A. Class, M. E. Rickert, H. Larsson, P. Lichtenstein, and B. M. D'Onofrio, "Fetal growth and psychiatric and socioeconomic problems: Population-based sibling comparison," *British Journal of Psychiatry*, vol. 205, no. 5, pp. 355–361, Nov. 2014. DOI: 10.1192/bjp.bp.113.143693.

[35] J. M. Perlman, "Neurobehavioral Deficits in Premature Graduates of Intensive Care—Potential Medical and Neonatal Environmental Risk Factors," *Pediatrics*, vol. 108, no. 6, pp. 1339–1348, Dec. 2001. DOI: 10.1542/PEDS.108.6.1339. [Online]. Available: /pediatrics/article/108/6/1339/63618/Neurobehavioral-Deficits-in-Premature-Graduates-of%20https://publications.aap.org/pediatrics/article/108/6/1339/63618/Neurobehavioral-Deficits-in-Premature-Graduates-of.

[36] L. J. Abernethy, M. Palaniappan, and R. W. Cooke, "Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight," *Archives of disease in childhood*, vol. 87, no. 4, pp. 279–283, Oct. 2002. DOI: 10.1136/ADC.87.4.279. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/12243993/.

[37] J. L. Daval *et al.*, "Neonatal Hypoxia Triggers Transient Apoptosis Followed by Neurogenesis in the Rat CA1 Hippocampus," *Pediatric Research 2004 55:4*, vol. 55, no. 4, pp. 561–567, 2004. DOI: 10.1203/01.pdr.0000113771.51317.37. [Online]. Available: https://www.nature.com/articles/pr200488.

[38] T. E. Froehlich, J. S. Anixt, I. M. Loe, V. Chirdkiatgumchai, L. Kuan, and R. C. Gilman, "Update on environmental risk factors for attention-deficit/hyperactivity disorder," *Current Psychiatry Reports*, vol. 13, no. 5, pp. 333–344, Oct. 2011. DOI: 10.1007/s11920-011-0221-3.

[39] A. E. Russell, T. Ford, R. Williams, and G. Russell, *The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review*, Jun. 2016. DOI: 10.1007/s10578-015-0578-3.

[40] G. Fanjiang and R. E. Kleinman, "Nutrition and performance in children," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 10, no. 3, pp. 342–347, May 2007. DOI: 10.1097/MCO.0B013E3280523A9E. [Online]. Available: https://journals.lww.com/co-clinicalnutrition/Fulltext/2007/05000/Nutrition_and_performance_in_children.14.aspx.

[41] E. Mick, J. Biederman, S. V. Faraone, J. Sayer, and S. Kleinman, "Case-Control Study of Attention-Deficit Hyperactivity Disorder and Maternal Smoking, Alcohol Use, and Drug Use During Pregnancy," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 41, no. 4, pp. 378–385, Apr. 2002. DOI: 10.1097/00004583-200204000-00009.

[42] S. V. Faraone *et al.*, *Molecular genetics of attention-deficit/hyperactivity disorder*, Jun. 2005. DOI: 10.1016/j.biopsych.2004.11.024.

[43] Q. Chen *et al.*, "Familial aggregation of attention-deficit/hyperactivity disorder," *Journal of Child Psychology and Psychiatry and Allied Disciplines*, vol. 58, no. 3, pp. 231–239, Mar. 2017. DOI: 10.1111/jcpp.12616.

[44] I. R. Gizer, C. Ficks, and I. D. Waldman, *Candidate gene studies of ADHD: A meta-analytic review*, 2009. DOI: 10.1007/s00439-009-0694-x.

[45] S. V. Faraone and E. Mick, *Molecular genetics of attention deficit hyperactivity disorder*, Mar. 2010. DOI: 10.1016/j.psc.2009.12.004.

[46] A. Thapar, M. Cooper, O. Eyre, and K. Langley, *Practitioner review: What have we learnt about the causes of ADHD?* Jan. 2013. DOI: 10.1111/j.1469-7610.2012.02611.x.

[47] E. Uffelmann *et al.*, *Genome-wide association studies*, Dec. 2021. DOI: 10.1038/s43586-021-00056-9.

[48] B. M. Neale *et al.*, "Meta-analysis of genome-wide association studies of attention-deficit/ hyperactivity disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 49, no. 9, pp. 884–897, Sep. 2010. DOI: 10.1016/j.jaac.2010.06.008.

[49] D. Demontis *et al.*, "Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder," *Nature Genetics 2018 51:1*, vol. 51, no. 1, pp. 63–75, Nov. 2018. DOI: 10.1038/s41588-018-0269-7. [Online]. Available: https://www.nature.com/articles/s41588-018-0269-7.

[50] A. Thapar, *Discoveries on the genetics of ADHD in the 21st century: New findings and their implications*, Oct. 2018. DOI: 10.1176/appi.ajp.2018.18040383.

[51] J. Nigg, M. Nikolas, and S. A. Burt, "Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 49, no. 9, pp. 863–873, Sep. 2010. DOI: 10.1016/j.jaac.2010.01.025. [Online]. Available: http://www.jaacap.org/article/S0890856710002893/fulltext%20http://www.jaacap.org/article/S0890856710002893/abstract%20https://www.jaacap.org/article/S0890-8567(10)00289-3/abstract.

[52] V. S. Palladino, R. McNeill, A. Reif, and S. Kittel-Schneider, *Genetic risk factors and gene-environment interactions in adult and childhood attention-deficit/hyperactivity disorder*, Jun. 2019. DOI: 10.1097/YPG.0000000000000220.

[53] J. Martin, M. L. Hamshere, E. Stergiakouli, M. C. O'Donovan, and A. Thapar, "Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population," *Biological Psychiatry*, vol. 76, no. 8, pp. 664–671, Oct. 2014. DOI: 10.1016/j.biopsych.2014.02.013.

[54] E. Stergiakouli *et al.*, "Shared genetic influences between attention-deficit/hyperactivity disorder (ADHD) traits in children and clinical ADHD," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 54, no. 4, pp. 322–327, Apr. 2015. DOI: 10.1016/j.jaac.2015.01.010.

[55] M. M. Groen-Blokhuis *et al.*, "Attention-deficit/hyperactivity disorder polygenic risk scores predict attention problems in a population-based sample of children," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 53, no. 10, pp. 1123–1129, Oct. 2014. DOI: 10.1016/j.jaac.2014.06.014.

[56] C. M. Middeldorp *et al.*, "A Genome-Wide Association Meta-Analysis of Attention-Deficit/Hyperactivity Disorder Symptoms in Population-Based Pediatric Cohorts," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 55, no. 10, pp. 896–905, Oct. 2016. DOI: 10.1016/J.JAAC.2016.05.025.

[57] R. Bussing, D. M. Mason, L. Bell, P. Porter, and C. Garvan, "Adolescent Outcomes of Childhood Attention-Deficit/Hyperactivity Disorder in a Diverse Community Sample," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 49, no. 6, pp. 595–605, Jun. 2010. DOI: 10.1016/j.jaac.2010.03.006.

[58] W. J. Barbaresi, R. C. Colligan, A. L. Weaver, R. G. Voigt, J. M. Killian, and S. K. Katusic, *Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: A prospective study*, Apr. 2013. DOI: 10.1542/peds.2012-2354.

[59] J. S. Brook, D. W. Brook, C. Zhang, N. Seltzer, and S. J. Finch, "Adolescent ADHD and adult physical and mental health, work performance, and financial stress," *Pediatrics*, vol. 131, no. 1, pp. 5–13, 2013. DOI: 10.1542/peds.2012-1725.

[60] NICE., *Attention deficit hyperactivity disorder: diagnosis and management.* 2018. [Online]. Available: https://www.nice.org.uk/guidance/ng87.

[61] S. Pliszka, "Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 46, no. 7, pp. 894–921, Jul. 2007. DOI: 10.1097/CHI.0B013E318054E724. [Online]. Available: http://www.jaacap.org/article/S0890856709621821/fulltext%20http://www.jaacap.org/article/S0890856709621821/abstract%20https://www.jaacap.org/article/S0890-8567(09)62182-1/abstract.

[62] J. D. Palacio, F. De La Peña-Olvera, L. Palacios-Cruz, and S. Ortiz-León, "35 S Algoritmo latinoamericano de tratamiento multimodal del trastorno por déficit de atención e hiperactividad (TDAH) a través de la vida," Tech. Rep. 1, 2009.

[63] J. Posner, V. Rauh, A. Gruber, I. Gat, Z. Wang, and B. S. Peterson, "Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder," *Psychiatry Research - Neuroimaging*, vol. 213, no. 1, pp. 24–30, Jul. 2013. DOI: 10.1016/j.pscychresns.2013.01.004.

[64] S. V. Faraone and J. Buitelaar, "Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis," *European Child and Adolescent Psychiatry*, vol. 19, no. 4, pp. 353–364, Apr. 2010. DOI: 10.1007/s00787-009-0054-3.

[65] X. Castells *et al.*, "Efficacy of Methylphenidate for Adults with Attention-Deficit Hyperactivity Disorder," *CNS Drugs 2011 25:2*, vol. 25, no. 2, pp. 157–169, Aug. 2012. DOI: 10.2165/11539440-000000000-00000. [Online]. Available: https://link.springer.com/article/10.2165/11539440-000000000-00000.

[66] S. Cortese *et al.*, "Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis," *The Lancet Psychiatry*, vol. 5, no. 9, pp. 727–738, Sep. 2018. DOI: 10.1016/S2215-0366(18)30269-4.

[67] H. M. Schachter, B. Pham, J. King, S. Langford, and D. Moher, "How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis," *CMAJ: Canadian Medical Association Journal*, vol. 165, no. 11, p. 1475, Nov. 2001. [Online]. Available: /pmc/articles/PMC81663/%20/pmc/articles/PMC81663/?report=abstract%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC81663/.

[68] S. Schwartz and C. U. Correll, "Efficacy and safety of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: Results from a comprehensive meta-analysis and metaregression," *Journal of the American Academy*

of Child and Adolescent Psychiatry, vol. 53, no. 2, pp. 174–187, Feb. 2014. DOI: 10.1016/j.jaac.2013.11.005.

[69] T. E. Wilens *et al.*, "A Randomized, Placebo-Controlled Trial of Guanfacine Extended Release in Adolescents With Attention-Deficit/Hyperactivity Disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 54, no. 11, pp. 916–925, Nov. 2015. DOI: 10.1016/j.jaac.2015.08.016.

[70] L. Scahill *et al.*, "A Placebo-Controlled Study of Guanfacine in the Treatment of Children With Tic Disorders and Attention Deficit Hyperactivity Disorder," Tech. Rep., 2001, p. 7.

[71] P. Lichtenstein *et al.*, "Medication for Attention Deficit–Hyperactivity Disorder and Criminality," *New England Journal of Medicine*, vol. 367, no. 21, pp. 2006–2014, Nov. 2012. DOI: 10.1056/nejmoa1203241.

[72] Z. Chang *et al.*, "Association between medication use for attention-deficit/hyperactivity disorder and risk of motor vehicle crashes," *JAMA Psychiatry*, vol. 74, no. 6, pp. 597–603, Jun. 2017. DOI: 10.1001/jamapsychiatry.2017.0659.

[73] M. J. Lee *et al.*, "Attention-deficit hyperactivity disorder, its treatment with medication and the probability of developing a depressive disorder: A nationwide population-based study in Taiwan," *Journal of Affective Disorders*, vol. 189, pp. 110–117, Jan. 2016. DOI: 10.1016/j.jad.2015.09.015.

[74] B. S. Molina *et al.*, "The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 48, no. 5, pp. 484–500, May 2009. DOI: 10.1097/CHI.0b013e31819c23d0. [Online]. Available: http://www.jaacap.org/article/S0890856709600666/fulltext%20http://www.jaacap.org/article/S0890856709600666/abstract%20https://www.jaacap.org/article/S0890-8567(09)60066-6/abstract.

[75] E. Chan, J. M. Fogler, and P. G. Hammerness, *Treatment of attention-deficit/hyperactivity disorder in adolescents: A systematic review*, May 2016. DOI: 10.1001/jama.2016.5453.

[76] A. F. Kortekaas-Rijlaarsdam, M. Luman, E. Sonuga-Barke, and J. Oosterlaan, *Does methylphenidate improve academic performance? A systematic review and meta-analysis*, Feb. 2019. DOI: 10.1007/s00787-018-1106-3.

[77] A. Charach and R. Fernandez, "Enhancing ADHD medication adherence: Challenges and opportunities topical collection on attention-deficit disorder," *Current Psychiatry Reports*, vol. 15, no. 7, Jul. 2013. DOI: 10.1007/s11920-013-0371-6.

[78] D. E. Greydanus, A. N. Dilip, and R. Patel, "Psychopharmacology of ADHD in pediatrics: current advances and issues," Tech. Rep., 2009, pp. 5–171.

[79] M. L. Rimestad, R. Lambek, H. Zacher Christiansen, and E. Hougaard, *Short- and Long-Term Effects of Parent Training for Preschool Children With or at Risk of ADHD: A Systematic Review and Meta-Analysis*, Mar. 2019. DOI: 10.1177/1087054716648775.

[80] S. Cortese *et al.*, *Cognitive training for attention-deficit/hyperactivity disorder: Meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials*, Mar. 2015. DOI: 10.1016/j.jaac.2014.12.010.

[81] S. Cortese *et al.*, *Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials*, Jun. 2016. DOI: 10.1016/j.jaac.2016.03.007.

[82] B. S. Molina *et al.*, "The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 48, no. 5, pp. 484–500, 2009. DOI: 10.1097/CHI.0b013e31819c23d0.

[83] J. T. Nigg and B. J. Casey, "An integrative theory of attention-deficit/ hyperactivity disorder based on the cognitive and affective neurosciences," *Development and Psychopathology*, vol. 17, no. 3, pp. 785–806, Jul. 2005. DOI: 10.1017/S0954579405050376. [Online]. Available: https://www.cambridge.org/core/journals/development-and-psychopathology/article/abs/an-integrative-theory-of-attentiondeficit-hyperactivity-disorder-based-on-the-cognitive-and-affective-neurosciences/64C94E30EECCA5F2A586600E0D6605C1.

[84] J. T. Nigg, "Neuropsychologic Theory and Findings in Attention-Deficit/Hyperactivity Disorder: The State of the Field and Salient Challenges for the Coming Decade," *Biological Psychiatry*, vol. 57, no. 11, pp. 1424–1435, Jun. 2005. DOI: 10.1016/J.BIOPSYCH.2004.11.011. [Online]. Available: http://www.biologicalpsychiatryjournal.com/article/S0006322304011771/fulltext%20http://www.biologicalpsychiatryjournal.com/article/S0006322304011771/abstract%20https://www.biologicalpsychiatryjournal.com/article/S0006-3223(04)01177-1/abstract.

[85] D. Sjöwall, L. Roth, S. Lindqvist, and L. B. Thorell, "Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits," *Journal of Child Psychology and Psychiatry*, vol. 54, no. 6, pp. 619–627, Jun. 2013. DOI: 10.1111/JCPP.12006. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1111/jcpp.12006%20https://onlinelibrary.wiley.com/doi/abs/10.1111/jcpp.12006%20https://acamh.onlinelibrary.wiley.com/doi/10.1111/jcpp.12006.

[86] B. F. Pennington and S. Ozonoff, "Executive functions and developmental psychopathology," *Journal of Child Psychology and Psychiatry and Allied Disciplines*, vol. 37, no. 1, pp. 51–87, Jan. 1996. DOI: 10.1111/J.1469-7610.1996.TB01380.X. [Online]. Available: /record/1996-01725-004.

[87] R. A. Barkley, "Behavioral Inhibition, Sustained Attention, and Executive Functions: Constructing a Unifying Theory of ADHD," Tech. Rep. 1, 1997, pp. 65–94.

[88] M. A. Pievsky and R. E. McGrath, *The Neurocognitive Profile of Attention-Deficit/Hyperactivity Disorder: A Review of Meta-Analyses*, Mar. 2018. DOI: 10.1093/arclin/acx055.

[89] G. Tripp and B. Alsop, "Sensitivity to Reward Frequency in Boys With Attention Deficit Hyperactivity Disorder," *https://doi.org/10.1207/S15374424jccp280309*, vol. 28, no. 3, pp. 366–375, 2010. DOI: 10.1207/S15374424JCCP280309. [Online]. Available: https://www.tandfonline.com/doi/abs/10.1207/S15374424jccp280309.

[90] Z. R. Smith and J. M. Langberg, *Review of the Evidence for Motivation Deficits in Youth with ADHD and Their Association with Functional Outcomes*, Dec. 2018. DOI: 10.1007/s10567-018-0268-3.

[91] A. Diamond, "Attention-deficit disorder (attention-deficit/ hyperactivity disorder without hyperactivity): A neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity)," *Development and Psychopathology*, vol. 17, no. 3, pp. 807–825, Jul. 2005. DOI: 10.1017/S0954579405050388. [Online]. Available: https://www.cambridge.org/core/journals/development-and-psychopathology/article/abs/attentiondeficit-disorder-attentiondeficit-hyperactivity-disorder-without-hyperactivity-a-neurobiologically-and-behaviorally-distinct-disorder-from-attentiondeficithyperactivity-disorder-with-hyperactivity/A514B3DD207C6B037

[92] J. Kuntsi *et al.*, "Co-Occurrence of ADHD and Low IQ Has Genetic Origins," *American Journal of Medical Genetics - Neuropsychiatric Genetics*, vol. 124 B, no. 1, pp. 41–47, Jan. 2004. DOI: 10.1002/ajmg.b.20076.

[93] J. Zhang *et al.*, "What have we really learned from functional connectivity in clinical populations?" *NeuroImage*, vol. 242, Nov. 2021. DOI: 10.1016/j.neuroimage.2021.118466.

[94] V. P. Grover, J. M. Tognarelli, M. M. Crossey, I. J. Cox, S. D. Taylor-Robinson, and M. J. McPhail, *Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians*, Sep. 2015. DOI: 10.1016/j.jceh.2015.08.001.

[95] S. Ogawa, T. M. Lee, A. R. Kay, and D. W. Tank, "Brain magnetic resonance imaging with contrast dependent on blood oxygenation (cerebral blood flow/brain metabolism/oxygenation)," Tech. Rep., 1990, pp. 9868–9872.

[96] N. K. Logothetis, "Neurovascular uncoupling: Much ado about nothing," *Frontiers in Neuroenergetics*, vol. 0, p. 2, 2010. DOI: 10.3389/FNENE.2010.00002.

[97] H. Girouard and C. Iadecola, "Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease," *Journal of Applied Physiology*, vol. 100, no. 1, pp. 328–335, Jan. 2006. DOI: 10.1152/JAPPLPHYSIOL.00966.2005/ASSET/IMAGES/LARGE/ZDG0010663230001.JPEG. [Online]. Available: https://journals.physiology.org/doi/10.1152/japplphysiol.00966.2005.

[98] Y. B. Sirotin and A. Das, "Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity," *Nature 2009 457:7228*, vol. 457, no. 7228, pp. 475–479, Jan. 2009. DOI: 10.1038/nature07664. [Online]. Available: https://www.nature.com/articles/nature07664.

[99] D. Attwell, A. M. Buchan, S. Charpak, M. Lauritzen, B. A. MacVicar, and E. A. Newman, "Glial and neuronal control of brain blood flow," *Nature 2010 468:7321*, vol. 468, no. 7321, pp. 232–243, Nov. 2010. DOI: 10.1038/nature09613. [Online]. Available: https://www.nature.com/articles/nature09613.

[100] K. J. Worsley and K. J. Friston, "Analysis of fMRI Time-Series Revisited—Again," *NeuroImage*, vol. 2, no. 3, pp. 173–181, Sep. 1995. DOI: 10.1006/NIMG.1995.1023.

[101] R. L. Buckner *et al.*, "Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging (neuroimagingsingle triallanguageprefrontal)," Tech. Rep., 1996, pp. 14 878–14 883.

[102] K. J. Friston, E. Zarahn, O. Josephs, R. N. Henson, and A. M. Dale, "Stochastic Designs in Event-Related fMRI," *NeuroImage*, vol. 10, no. 5, pp. 607–619, Nov. 1999. DOI: 10.1006/NIMG.1999.0498.

[103] B. Biswal, F. Zerrin Yetkin, V. M. Haughton, and J. S. Hyde, "Functional connectivity in the motor cortex of resting human brain using echo-planar mri," *Magnetic Resonance in Medicine*, vol. 34, no. 4, pp. 537–541, Oct. 1995. DOI: 10.1002/MRM.1910340409. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1002/mrm.1910340409%20https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.1910340409%20https://onlinelibrary.wiley.com/doi/10.1002/mrm.1910340409.

[104] B. B. Biswal, J. V. Kylen, and J. S. Hyde, "Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps," *NMR in Biomedicine*, vol. 10, no. 4-5, pp. 165–170, Jun. 1997. DOI: 10.1002/(SICI)1099-1492(199706/08)10:4/5<165::AID-NBM454>3.0.CO;2-7.

[105] M. H. Lee, C. D. Smyser, and J. S. Shimony, "Resting-state fMRI: A review of methods and clinical applications," *American Journal of Neuroradiology*, vol. 34, no. 10, pp. 1866–1872, Oct. 2013. DOI: 10.3174/ajnr.A3263.

[106] K. J. Friston, "Functional and Effective Connectivity: A Review," *Brain Connectivity*, vol. 1, no. 1, pp. 13–36, 2011. DOI: 10.1089/brain.2011.0008.

[107] A. M. Bastos and J. M. Schoffelen, *A tutorial review of functional connectivity analysis methods and their interpretational pitfalls*, Jan. 2016. DOI: 10.3389/fnsys.2015.00175.

[108] S. Ramón y Cajal, P. Pasik, and T. Pasik, "Texture of the nervous system of man and the vertebrates," 1999.

[109] A. Backlund, "The definition of system," *Kybernetes*, vol. 29, no. 4, pp. 444–451, Jun. 2000. DOI: 10.1108/03684920010322055/FULL/XML.

[110] R. Descartes, "Discourse on the Method," *Descartes: Selected Philosophical Writings*, pp. 20–56, May 2013. DOI: 10.1017/CBO9780511805059.004.

[111] R. Descartes, "Meditations on First Philosophy," *Descartes: Selected Philosophical Writings*, pp. 73–122, May 2013. DOI: 10.1017/CBO9780511805059.006.

[112] D. D. Chene, "Spirits and Clocks: Machine and Organism in Descartes," *The Philosophical Quarterly*, vol. 52, no. 209, pp. 632–662, Oct. 2001. DOI: 10.1111/1467-9213.T01-1-00290. [Online]. Available: https://philpapers.org/rec/DESSAC-3.

[113] J. S. Mill, "A System of Logic, Ratiocinative and Inductive: Being a Connected View of the Principles of Evidence, and the Methods of Scientific Investigation," *A System of Logic, Ratiocinative and Inductive*, Dec. 2011. DOI: 10.1017/CBO9781139149839. [Online]. Available: https://www.cambridge.org/core/books/system-of-logic-ratiocinative-and-inductive/290C43FBA4DC7022540D

[114] L. V. Bertalanffy, "An outline of general system theory," *British Journal for the Philosophy of Science*, vol. 1, no. 2, pp. 134–165, Aug. 1950. DOI: 10.1093/BJPS/I.2.134. [Online]. Available: https://philpapers.org/rec/VONAOO-2.

[115] A. Montuori, "The Systems Approach to Creativity," *Montuori A. (2011) Systems Approach. In: Runco MA, and Pritzker SR (eds.)Encyclopedia of Creativity, Second Edition, vol. 2, pp. 414-421 San Diego:Academic Press.*, Jan. 2011. [Online]. Available: https://www.academia.edu/1067750/The_Systems_Approach_to_Creativity.

[116] A. F. Siegenfeld and Y. Bar-Yam, "An Introduction to Complex Systems Science and Its Applications," *Complexity*, vol. 2020, 2020. DOI: 10.1155/2020/6105872.

[117] M. Koutrouli, E. Karatzas, D. Paez-Espino, and G. A. Pavlopoulos, *A Guide to Conquer the Biological Network Era Using Graph Theory*, Jan. 2020. DOI: 10.3389/fbioe.2020.00034.

[118] L. Euler, "Solutio problematis ad geometriam situs pertinentis," *Commentarii academiae scientiarum Petropolitanae*, Jan. 1741. [Online]. Available: https://scholarlycommons.pacific.edu/euler-works/53.

[119] U. Brandes and T. Erlebach, Eds., *Network Analysis*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2005, vol. 3418. DOI: 10.1007/b106453.

[120] M. Kivelä, A. Arenas, M. Barthelemy, J. P. Gleeson, Y. Moreno, and M. A. Porter, "Multilayer networks," *Journal of Complex Networks*, vol. 2, no. 3, pp. 203–271, Sep. 2014. DOI: 10.1093/comnet/cnu016.

[121] D. Zhou, J. Huang, and B. Schölkopf, "Learning with Hypergraphs: Clustering, Classification, and Embedding," in *Advances in Neural Information Processing Systems*, B. Schölkopf, J. Platt, and T. Hoffman, Eds., vol. 19, MIT Press, 2006. [Online]. Available: https://proceedings.neurips.cc/paper/2006/file/dff8e9c2ac33381546d96deea9922999-Paper.pdf.

[122] M. Vaiana and S. F. Muldoon, "Multilayer Brain Networks," *Journal of Nonlinear Science*, vol. 30, no. 5, pp. 2147–2169, Oct. 2020. DOI: 10.1007/s00332-017-9436-8.

[123] E. Bullmore and O. Sporns, *Complex brain networks: Graph theoretical analysis of structural and functional systems*, Mar. 2009. DOI: 10.1038/nrn2575.

[124] M. E. J. Newman, "The structure and function of complex networks," Tech. Rep., 2003.

[125] D. J. Watts and S. H. Strogatz, "Collective dynamics of 'small-world' networks," *Nature 1998 393:6684*, vol. 393, no. 6684, pp. 440–442, Jun. 1998. DOI: 10.1038/30918. [Online]. Available: https://www.nature.com/articles/30918.

[126] R. L. Buckner *et al.*, "Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease," *Journal of Neuroscience*, 2009. DOI: 10.1523/JNEUROSCI.5062-08.2009.

[127] J. G. White, E. Southgate, J. Thomson, and S. Brenner, "The structure of the nervous system of the nematode Caenorhabditis elegans," *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, vol. 314, no. 1165, pp. 1–340, Nov. 1986. DOI: 10.1098/rstb.1986.0056.

[128] J. H. Downes *et al.*, "Emergence of a small-world functional network in cultured neurons," *PLoS Computational Biology*, vol. 8, no. 5, May 2012. DOI: 10.1371/journal.pcbi.1002522.

[129] P. Hagmann *et al.*, "Mapping human whole-brain structural networks with diffusion MRI," *PLoS ONE*, vol. 2, no. 7, Jul. 2007. DOI: 10.1371/journal.pone.0000597.

[130] P. Hagmann *et al.*, "Mapping the structural core of human cerebral cortex," *PLoS Biology*, vol. 6, no. 7, pp. 1479–1493, Jul. 2008. DOI: 10.1371/journal.pbio.0060159.

[131] Y. Iturria-Medina, R. C. Sotero, E. J. Canales-Rodríguez, Y. Alemán-Gómez, and L. Melie-García, "Studying the human brain anatomical network via diffusion-weighted MRI and Graph Theory," *NeuroImage*, vol. 40, no. 3, pp. 1064–1076, Apr. 2008. DOI: 10.1016/j.neuroimage.2007.10.060.

[132] R. Salvador, J. Suckling, M. R. Coleman, J. D. Pickard, D. Menon, and E. Bullmore, "Neurophysiological Architecture of Functional Magnetic Resonance Images of Human Brain," *Cerebral Cortex*, vol. 15, no. 9, pp. 1332–1342, Sep. 2005. DOI: 10.1093/CERCOR/BHI016. [Online]. Available: https://academic.oup.com/cercor/article/15/9/1332/288667.

[133] S. Achard, R. Salvador, B. Whitcher, J. Suckling, and E. Bullmore, "A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs," *Journal of Neuroscience*, vol. 26, no. 1, pp. 63–72, Jan. 2006. DOI: 10.1523/JNEUROSCI.3874-05.2006. [Online]. Available: https://www.jneurosci.org/content/26/1/63%20https://www.jneurosci.org/content/26/1/63.abstract.

[134] M. Valencia, J. Martinerie, S. Dupont, and M. Chavez, "Dynamic small-world behavior in functional brain networks unveiled by an event-related networks approach," *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, vol. 77, no. 5, p. 050 905, May 2008. DOI: 10.1103/PHYSREVE.77.050905/FIGURES/4/MEDIUM. [Online]. Available: https://journals.aps.org/pre/abstract/10.1103/PhysRevE.77.050905.

[135] J. Wang *et al.*, "Parcellation-dependent small-world brain functional networks: A resting-state fmri study," *Human Brain Mapping*, vol. 30, no. 5, pp. 1511–1523, May 2009. DOI: 10.1002/HBM.20623.

[136] D. S. Bassett and E. T. Bullmore, *Small-World Brain Networks Revisited*, Oct. 2017. DOI: 10.1177/1073858416667720.

[137] E. Bullmore and O. Sporns, *The economy of brain network organization*, May 2012. DOI: 10.1038/nrn3214.

[138] A. Avena-Koenigsberger *et al.*, "Using Pareto optimality to explore the topology and dynamics of the human connectome," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 369, no. 1653, Oct. 2014. DOI: 10.1098/rstb.2013.0530.

[139] D. A. Fair *et al.*, "Development of distinct control networks through segregation and integration," *Proceedings of the National Academy of Sciences of the United States of America*, 2007. DOI: 10.1073/pnas.0705843104.

[140] Z. Yao, B. Hu, Y. Xie, P. Moore, and J. Zheng, *A review of structural and functional brain networks: small world and atlas*, Mar. 2015. DOI: 10.1007/s40708-015-0009-z.

[141] D. H. Weissman, K. C. Roberts, K. M. Visscher, and M. G. Woldorff, "The neural bases of momentary lapses in attention," *Nature Neuroscience*, vol. 9, no. 7, pp. 971–978, 2006. DOI: 10.1038/nn1727.

[142] E. M. El-Sayed and Karolinska University Press), "Brain maturation, cognitive tasks, and quantitative electroencephalography : A study in children with attention deficit hyperactive disorder," Dec. 2002. [Online]. Available: http://openarchive.ki.se/xmlui/handle/10616/39995.

[143] M. Kinsbourne, "MINIMAL BRAIN DYSFUNCTION AS A NEURODEVELOPMENTAL LAG," *Annals of the New York Academy of Sciences*, vol. 205, no. 1, pp. 268–273, 1973. DOI: https://doi.org/10.1111/j.1749-6632.1973.tb43184.x. [Online]. Available: https://nyaspubs.onlinelibrary.wiley.com/doi/abs/10.1111/j.1749-6632.1973.tb43184.x.

[144] P. Shaw *et al.*, "Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation," *Proceedings of the National Academy of Sciences of the United States of America*, 2007. DOI: 10.1073/pnas.0707741104.

[145] J. Stiles and T. L. Jernigan, *The basics of brain development*, Dec. 2010. DOI: 10.1007/s11065-010-9148-4.

[146] A. W. Toga, P. M. Thompson, and E. R. Sowell, "Mapping brain maturation," *Trends in Neurosciences*, vol. 29, no. 3, pp. 148–159, Mar. 2006. DOI: 10.1016/j.tins.2006.01.007. [Online]. Available: http://www.cell.com/article/S0166223606000245/fulltext%20http://www.cell.com/article/S0166223606000245/abstract%20https://www.cell.com/trends/neurosciences/abstract/S0166-2236(06)00024-5.

[147] K. A. Nave and H. B. Werner, "Myelination of the nervous system: Mechanisms and functions," in *Annual Review of Cell and Developmental Biology*, vol. 30, Annual Reviews Inc., 2014, pp. 503–533. DOI: 10.1146/annurev-cellbio-100913-013101.

[148] L. Marner, J. R. Nyengaard, Y. Tang, and B. Pakkenberg, "Marked loss of myelinated nerve fibers in the human brain with age," *Journal of Comparative Neurology*, vol. 462, no. 2, pp. 144–152, Jul. 2003. DOI: 10.1002/cne.10714.

[149] C. A. Mann, J. F. Lubar, A. W. Zimmerman, C. A. Miller, and R. A. Muenchen, "Quantitative analysis of EEG in boys with attention-deficit-hyperactivity disorder: Controlled study with clinical implications," *Pediatric Neurology*, vol. 8, no. 1, pp. 30–36, Jan. 1992. DOI: 10.1016/0887-8994(92)90049-5. [Online]. Available: http://www.pedneur.com/article/0887899492900495/fulltext%20http://www.pedneur.com/article/0887899492900495/abstract%20https://www.pedneur.com/article/0887-8994(92)90049-5/abstract.

[150] K. G. SIEG, G. R. GAFFNEY, D. F. PRESTON, and J. A. HELLINGS, "SPECT Brain Imaging Abnormalities in Attention Deficit Hyperactivity Disorder," *Clinical Nuclear Medicine*, vol. 20, no. 1, pp. 55–60, Jan. 1995. DOI: 10.1097/00003072-199501000-00014.

[151] P. Shaw *et al.*, "Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder," *Archives of General Psychiatry*, 2006. DOI: 10.1001/archpsyc.63.5.540.

[152] P. Shaw, N. Gogtay, and J. Rapoport, *Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories*, 2010. DOI: 10.1002/hbm.21028.

[153] P. Shaw, M. Malek, B. Watson, D. Greenstein, P. De Rossi, and W. Sharp, "Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder," *Biological Psychiatry*, 2013. DOI: 10.1016/j.biopsych.2013.04.007.

[154] C. S. Sripada, D. Kessler, and M. Angstadt, "Lag in maturation of the brain's intrinsic functional architecture in attention-deficit/hyperactivity disorder," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 39, pp. 14 259–14 264, 2014. DOI: 10.1073/pnas.1407787111.

[155] J. R. Sato, M. Q. Hoexter, X. F. Castellanos, and L. A. Rohde, "Abnormal Brain Connectivity Patterns in Adults with ADHD: A Coherence Study," *PLoS ONE*, vol. 7, no. 9, Sep. 2012. DOI: 10.1371/journal.pone.0045671.

[156] J. Choi, B. Jeong, S. W. Lee, and H. J. Go, "Aberrant Development of Functional Connectivity among Resting State-Related Functional Networks in Medication-Naïve ADHD Children," *PLOS ONE*, vol. 8, no. 12, e83516, Feb. 2013. DOI: 10.1371/JOURNAL.PONE.0083516. [Online]. Available: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0083516.

[157] D. Kessler, M. Angstadt, and C. Sripada, "Growth Charting of Brain Connectivity Networks and the Identification of Attention Impairment in Youth," *JAMA Psychiatry*, vol. 73, no. 5, pp. 481–489, May 2016. DOI: 10.1001/JAMAPSYCHIATRY.2016.0088. [Online]. Available: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2513687.

[158] S. N. Haber, "The primate basal ganglia: parallel and integrative networks," *Journal of Chemical Neuroanatomy*, vol. 26, no. 4, pp. 317–330, Dec. 2003. DOI: 10.1016/J.JCHEMNEU.2003.10.003.

[159] A. Qiu *et al.*, "Basal ganglia volume and shape in children with attention deficit hyperactivity disorder," *American Journal of Psychiatry*, vol. 166, no. 1, pp. 74–82, Jan. 2009. DOI: 10.1176/APPI.AJP.2008.08030426/ASSET/IMAGES/LARGE/T915F3.JPEG. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2008.08030426.

[160] C. Shen *et al.*, "Neural Correlates of the Dual-Pathway Model for ADHD in Adolescents," *American Journal of Psychiatry*, vol. 177, no. 9, pp. 844–854, Sep. 2020. DOI: 10.1176/appi.ajp.2020.19020183.

[161] J. Posner *et al.*, "Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder," *Journal of the American Academy of Child and Adolescent Psychiatry*, vol. 50, no. 8, pp. 828–837, Aug. 2011. DOI: 10.1016/j.jaac.2011.05.010. [Online]. Available: http://www.jaacap.org/article/S0890856711004436/fulltext%20http://www.jaacap.org/article/S0890856711004436/abstract%20https://www.jaacap.org/article/S0890-8567(11)00443-6/abstract.

[162] S. Carmona *et al.*, "Response inhibition and reward anticipation in medication-naïve adults with attention-deficit/hyperactivity disorder: A within-subject case-control neuroimaging study," *Human Brain Mapping*, vol. 33, no. 10, pp. 2350–2361, Oct. 2012. DOI: 10.1002/HBM.21368.

[163] D. Tomasi and N. D. Volkow, "Abnormal functional connectivity in children with attention-deficit/ hyperactivity disorder," *Biological Psychiatry*, 2012. DOI: 10.1016/j.biopsych.2011.11.003.

[164] G. L. Shulman *et al.*, "Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex," *Journal of Cognitive Neuroscience*, vol. 9, no. 5, pp. 648–663, Oct. 1997. DOI: 10.1162/JOCN.1997.9.5.648. [Online]. Available: https://direct.mit.edu/jocn/article/9/5/648/3379/Common-Blood-Flow-Changes-across-Visual-Tasks-II.

[165] J. R. Andrews-Hanna, J. S. Reidler, J. Sepulcre, R. Poulin, and R. L. Buckner, "Functional-Anatomic Fractionation of the Brain's Default Network," *Neuron*, 2010. DOI: 10.1016/j.neuron.2010.02.005.

[166] S. Marek and N. U. F. Dosenbach, "The frontoparietal network: function, electrophysiology, and importance of individual precision mapping," Tech. Rep., 2018, pp. 133–140. [Online]. Available: www.dialogues-cns.org.

[167] F. X. Castellanos *et al.*, "Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/Hyperactivity Disorder," *Biological Psychiatry*, 2008. DOI: 10.1016/j.biopsych.2007.06.025.

[168] L. Sun *et al.*, "Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder," *Psychiatry Research - Neuroimaging*, 2012. DOI: 10.1016/j.pscychresns.2011.07.001.

[169] Y. Gao *et al.*, "Impairments of large-scale functional networks in attention-deficit/hyperactivity disorder: A meta-analysis of resting-state functional connectivity," *Psychological Medicine*, 2019. DOI: 10.1017/S003329171900237X.

[170] F. X. Castellanos and Y. Aoki, *Intrinsic Functional Connectivity in Attention-Deficit/Hyperactivity Disorder: A Science in Development*, 2016. DOI: 10.1016/j.bpsc.2016.03.004.

[171] V. Menon, *Salience Network*. Elsevier Inc., 2015, vol. 2, pp. 597–611. DOI: 10.1016/B978-0-12-397025-1.00052-X. [Online]. Available: http://dx.doi.org/10.1016/B978-0-12-397025-1.00052-X.

[172] D. Sridharan, D. J. Levitin, and V. Menon, "A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 34, pp. 12 569–12 574, Aug. 2008. DOI: 10.1073/PNAS.0800005105/SUPPL{_}FILE/0800005105SI.PDF. [Online]. Available: https://www.pnas.org/doi/abs/10.1073/pnas.0800005105.

[173] N. Goulden *et al.*, "The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM," *NeuroImage*, vol. 99, pp. 180–190, Oct. 2014. DOI: 10.1016/j.neuroimage.2014.05.052.

[174] V. Menon, "Brain networks and cognitive impairment in psychiatric disorders," *World Psychiatry*, vol. 19, no. 3, pp. 309–310, Oct. 2020. DOI: 10.1002/WPS.20799. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1002/wps.20799%20https://onlinelibrary.wiley.com/doi/abs/10.1002/wps.20799%20https://onlinelibrary.wiley.com/doi/10.1002/wps.20799.

[175] Q. Cao *et al.*, "Abnormal neural activity in children with attention deficit hyperactivity disorder: A resting-state functional magnetic resonance imaging study," *NeuroReport*, 2006. DOI: 10.1097/01.wnr.0000224769.92454.5d.

[176] L. Tian *et al.*, "Enhanced resting-state brain activities in ADHD patients: A fMRI study," *Brain and Development*, 2008. DOI: 10.1016/j.braindev.2007.10.005.

[177] D. Kessler, M. Angstadt, R. C. Welsh, and C. ipada, "Modality-spanning deficits in attention-deficit/ hyperactivity disorder in functional networks, Gray matter, And white matter," *Journal of Neuroscience*, 2014. DOI: 10.1523/JNEUROSCI.3156-14.2014.

[178] S. Carmona *et al.*, "Sensation-to-cognition cortical streams in attention-deficit/hyperactivity disorder," *Human Brain Mapping*, 2015. DOI: 10.1002/hbm.22790.

[179] J. Posner, G. V. Polanczyk, and E. Sonuga-Barke, *Attention-deficit hyperactivity disorder*, Feb. 2020. DOI: 10.1016/S0140-6736(19)33004-1.

[180] Milgram S., "The Small-World Problem," *Psychology Today*, vol. 1, no. 1, pp. 61–67, 1967.

[181] J. Travers and S. Milgram, "An Experimental Study of the Small World Problem," Tech. Rep. 4, 1969, pp. 425–443.

[182] J. Sepulcre, H. Liu, T. Talukdar, I. Martincorena, B. T. Thomas Yeo, and R. L. Buckner, "The organization of local and distant functional connectivity in the human brain," *PLoS Computational Biology*, 2010. DOI: 10.1371/journal.pcbi.1000808.

[183] J. Biederman, C. R. Petty, M. Evans, J. Small, and S. V. Faraone, "How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD," *Psychiatry Research*, 2010. DOI: 10.1016/j.psychres.2009.12.010.

[184] X. Cao *et al.*, "Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder," *Brain Research*, vol. 1303, pp. 195–206, Nov. 2009. DOI: 10.1016/J.BRAINRES.2009.08.029.

[185] E. Hoekzema *et al.*, "Stimulant drugs trigger transient volumetric changes in the human ventral striatum," *Brain Structure and Function 2012 219:1*, vol. 219, no. 1, pp. 23–34, Nov. 2012. DOI: 10.1007/S00429-012-0481-7. [Online]. Available: https://link.springer.com/article/10.1007/s00429-012-0481-7.

[186] H. Y. Lin *et al.*, "Brain–behavior patterns define a dimensional biotype in medication-naïve adults with attention-deficit hyperactivity disorder," *Psychological Medicine*, vol. 48, no. 14, pp. 2399–2408, Oct. 2018. DOI: 10.1017/S0033291718000028. [Online]. Available: https://www.cambridge.org/core/journals/psychological-medicine/article/abs/brainbehavior-patterns-define-a-dimensional-biotype-in-medicationnaive-adults-with-attentiondeficit-hyperactivity-disorder/BCBDAAFC48C3FE4A41CBEEE051D7FCDB.

[187] F. X. Castellanos and E. Proal, *Large-scale brain systems in ADHD: Beyond the prefrontal-striatal model*, 2012. DOI: 10.1016/j.tics.2011.11.007.

[188] H. Lin *et al.*, "Functional Connectivity of Attention-Related Networks in Drug-Naïve Children With ADHD," *Journal of Attention Disorders*, vol. 25, no. 3, pp. 377–388, Feb. 2021. DOI: 10.1177/1087054718802017. [Online]. Available: https://journals.sagepub.com/doi/10.1177/1087054718802017?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed.

[189] C. Keith Conners, G. Sitarenios, J. D. Parker, and J. N. Epstein, "The Revised Conners' Parent Rating Scale (CPRS-R): Factor Structure, Reliability, and Criterion Validity," *Journal of Abnormal Child Psychology 1998 26:4*, vol. 26, no. 4, pp. 257–268, 1998. DOI: 10.1023/A:1022602400621. [Online]. Available: https://link.springer.com/article/10.1023/A:1022602400621.

[190] M. F. Ward, P. H. Wender, and F. W. Reimherr, "The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder [published erratum appears in Am J Psychiatry 1993 Aug;150(8):1280]," *https://doi.org/10.1176/ajp.150.6.885*, vol. 150, no. 6, pp. 885–890, Apr. 2006. DOI: 10.1176/AJP.150.6.885. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/ajp.150.6.885.

[191] G. J. DuPaul, T. J. Power, A. D. Anastopoulos, and R. Reid, *ADHD Rating Scale—IV: Checklists, norms, and clinical interpretation.* 1998.

[192] M. B. First, M. Gibbon, R. Spitzer, and J. Williams, *User's guide for the structured clinical interview for DSM-IV axis I Disorders - Research version*. 1996.

[193] M. B. First, M. Gibbon, R. Spitzer, J. Williams, and L. Benjamin, "Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).," *American Psychiatric Press, Inc.*, 1997.

[194] D. Wechsler, *WAIS-III administration and scoring manual*. 1997.

[195] J. D. Power, K. A. Barnes, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen, "Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion," *NeuroImage*, 2012. DOI: 10.1016/j.neuroimage.2011.10.018.

[196] A. DiMartino *et al.*, *Unraveling the miswired connectome: A developmental perspective*, 2014. DOI: 10.1016/j.neuron.2014.08.050.

[197] R. Ciric *et al.*, "Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity," *NeuroImage*, 2017. DOI: 10.1016/j.neuroimage.2017.03.020.

[198] M. Jenkinson, P. Bannister, M. Brady, and S. Smith, "Improved optimization for the robust and accurate linear registration and motion correction of brain images," *NeuroImage*, 2002. DOI: 10.1016/S1053-8119(02)91132-8.

[199] J. D. Power, A. Mitra, T. O. Laumann, A. Z. Snyder, B. L. Schlaggar, and S. E. Petersen, "Methods to detect, characterize, and remove motion artifact in resting state fMRI," *NeuroImage*, vol. 84, pp. 320–341, Jan. 2014. DOI: 10.1016/J.NEUROIMAGE.2013.08.048.

[200] K. Murphy, R. M. Birn, D. A. Handwerker, T. B. Jones, and P. A. Bandettini, "The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced?" *NeuroImage*, 2009. DOI: 10.1016/j.neuroimage.2008.09.036.

[201] K. R. Van Dijk, T. Hedden, A. Venkataraman, K. C. Evans, S. W. Lazar, and R. L. Buckner, "Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization," *Journal of Neurophysiology*, 2010. DOI: 10.1152/jn.00783.2009.

[202] J. Schrouff *et al.*, "PRoNTo: Pattern recognition for neuroimaging toolbox," *Neuroinformatics*, vol. 11, no. 3, pp. 319–337, Jul. 2013. DOI: 10.1007/S12021-013-9178-1/FIGURES/11. [Online]. Available: https://link.springer.com/article/10.1007/s12021-013-9178-1.

[203] S. D. Forman, J. D. Cohen, M. Fitzgerald, W. F. Eddy, M. A. Mintun, and D. C. Noll, "Improved Assessment of Significant Activation in Functional Magnetic Resonance Imaging (fMRI): Use of a Cluster-Size Threshold," *Magnetic Resonance in Medicine*, vol. 33, no. 5, pp. 636–647, May 1995. DOI: 10.1002/MRM.1910330508. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1002/mrm.1910330508%20https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.1910330508%20https://onlinelibrary.wiley.com/doi/10.1002/mrm.1910330508.

[204] D. S. Marcus *et al.*, "Informatics and data mining tools and strategies for the human connectome project," *Frontiers in Neuroinformatics*, vol. 5, p. 4, Jun. 2011. DOI: 10.3389/FNINF.2011.00004/BIBTEX.

[205] L. Q. Uddin *et al.*, "Network homogeneity reveals decreased integrity of default-mode network in ADHD," *Journal of Neuroscience Methods*, vol. 169, no. 1, pp. 249–254, Mar. 2008. DOI: 10.1016/J.JNEUMETH.2007.11.031.

[206] B. S. Peterson *et al.*, "An fMRI study of the effects of psychostimulants on default-mode processing during stroop task performance in youths with ADHD," *American Journal of Psychiatry*, vol. 166, no. 11, pp. 1286–1294, Nov. 2009. DOI: 10.1176/APPI.AJP.2009.08050724/ASSET/IMAGES/LARGE/V116T3.JPEG. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2009.08050724.

[207] P. Shaw *et al.*, "Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder," *American Journal of Psychiatry*, vol. 168, no. 2, pp. 143–151, Feb. 2011. DOI: 10.1176/APPI.AJP.2010.10030385/ASSET/IMAGES/LARGE/APPI.AJP.2011.168.2.143D.JPEG. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2010.10030385.

[208] M. D. Fox, A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen, and M. E. Raichle, "The human brain is intrinsically organized into dynamic, anticorrelated functional networks," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 27, pp. 9673–9678, Jul. 2005. DOI: 10.1073/PNAS.0504136102/SUPPL{_}FILE/04136FIG5.PDF. [Online]. Available: https://www.pnas.org/doi/abs/10.1073/pnas.0504136102.

[209] D. A. Fair *et al.*, "The maturing architecture of the brain's default network," *Proceedings of the National Academy of Sciences*, vol. 105, no. 10, pp. 4028–4032,

Mar. 2008. DOI: 10.1073/pnas.0800376105. [Online]. Available: https://pnas.org/doi/full/10.1073/pnas.0800376105.

[210] H. Y. Lin, W. Y. I. Tseng, M. C. Lai, K. Matsuo, and S. S. F. Gau, "Altered Resting-State Frontoparietal Control Network in Children with Attention-Deficit/Hyperactivity Disorder," *Journal of the International Neuropsychological Society*, vol. 21, no. 4, pp. 271–284, Apr. 2015. DOI: 10.1017/S135561771500020X. [Online]. Available: https://www.cambridge.org/core/journals/journal-of-the-international-neuropsychological-society/article/abs/altered-restingstate-frontoparietal-control-network-in-children-with-attentiondeficithyperactivity-disorder/CBAB7AFFC237F0F3FD57A6DA28333F5C.

[211] V. Pereira and P. de Castro-Manglano, "The Effects of Medication on Default Mode Network (DMN) Connectivity in Attention Deficit/hyperactivity Disorder (ADHD): Bibliographic Review," *European Psychiatry*, 2017. DOI: 10.1016/j.eurpsy.2017.01.1022.

[212] A. Di Martino *et al.*, "Shared and Distinct Intrinsic Functional Network Centrality in Autism and Attention-Deficit/Hyperactivity Disorder," *Biological Psychiatry*, vol. 74, no. 8, pp. 623–632, Oct. 2013. DOI: 10.1016/J.BIOPSYCH.2013.02.011. [Online]. Available: http://www.biologicalpsychiatryjournal.com/article/S0006322313001765/fulltext%20http://www.biologicalpsychiatryjou
com/article/S0006322313001765/abstract%20https://www.biologicalpsychiatryjou
com/article/S0006-3223(13)00176-5/abstract.

[213] E. G. Duerden, R. Tannock, and C. Dockstader, "Altered cortical morphology in sensorimotor processing regions in adolescents and adults with attention-deficit/hyperactivity disorder," *Brain Research*, vol. 1445, pp. 82–91, Mar. 2012. DOI: 10.1016/j.brainres.2012.01.034.

[214] J. Sidlauskaite, E. Sonuga-Barke, H. Roeyers, and J. R. Wiersema, "Altered intrinsic organisation of brain networks implicated in attentional processes in adult attention-deficit/hyperactivity disorder: a resting-state study of attention, default mode and salience network connectivity," *European Archives of Psychiatry and Clinical Neuroscience 2015 266:4*, vol. 266, no. 4, pp. 349–357, Aug. 2015. DOI: 10.1007/S00406-015-0630-0. [Online]. Available: https://link.springer.com/article/10.1007/s00406-015-0630-0.

[215] S. Vossel, J. J. Geng, and G. R. Fink, "Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles," *Neuroscientist*, vol. 20, no. 2, pp. 150–159, Jul. 2014. DOI: 10.1177/1073858413494269. [Online]. Available: https://journals.sagepub.com/doi/10.1177/1073858413494269?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed.

[216] T. Silk *et al.*, "Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: Functional magnetic resonance imaging study," *The British Journal of Psychiatry*, vol. 187, no. 3, pp. 282–283, Sep. 2005. DOI: 10.1192/BJP.187.3.282. [Online]. Available: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/frontoparietal-activation-in-attentiondeficit-hyperactivity-disorder-combined-type-functional-magnetic-resonance-imaging-study/644FB4D5765AC34E13F79C42B53B6CA7.

[217] S. G. Dickstein, K. Bannon, F. Xavier Castellanos, and M. P. Milham, "The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis," *Journal of Child Psychology and Psychiatry*, vol. 47, no. 10, pp. 1051–1062, Nov. 2006. DOI: 10.1111/J.1469-7610.2006.01671.X. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1469-7610.2006.01671.x%20https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1469-7610.2006.01671.x%20https://acamh.onlinelibrary.wiley.com/doi/10.1111/j.1469-7610.2006.01671.x.

[218] T. J. Silk, A. Vance, N. Rinehart, J. L. Bradshaw, and R. Cunnington, "Dysfunction in the Fronto-Parietal Network in Attention Deficit Hyperactivity Disorder (ADHD): An fMRI Study," *Brain Imaging and Behavior 2008 2:2*, vol. 2, no. 2, pp. 123–131, Jan. 2008. DOI: 10.1007/S11682-008-9021-8. [Online]. Available: https://link.springer.com/article/10.1007/s11682-008-9021-8.

[219] S. J. Hong *et al.*, "Atypical functional connectome hierarchy in autism," *Nature Communications 2019 10:1*, vol. 10, no. 1, pp. 1–13, Mar. 2019. DOI: 10.1038/s41467-019-08944-1. [Online]. Available: https://www.nature.com/articles/s41467-019-08944-1.

[220] S. N. Visser *et al.*, "Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011," *Journal of the American Academy of Child and Adolescent Psychiatry*, 2014. DOI: 10.1016/j.jaac.2013.09.001.

[221] M. B. First, "Diagnostic and statistical manual of mental disorders, 5th edition, and clinical utility," *The Journal of nervous and mental disease*, vol. 201, no. 9, pp. 727–728, Sep. 2013. DOI: 10.1097/NMD.0B013E3182A2168A. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23995026/.

[222] K. Konrad and S. B. Eickhoff, "Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder," *Human Brain Mapping*, vol. 31, no. 6, pp. 904–916, Jun. 2010. DOI: 10.1002/HBM.21058. [Online]. Available: https://onlinelibrary.wiley.com/doi/full/10.1002/hbm.21058%20https://onlinelibrary.wiley.com/doi/

abs/10.1002/hbm.21058%20https://onlinelibrary.wiley.com/doi/10.1002/hbm.21058.

[223] M. Cao, N. Shu, Q. Cao, Y. Wang, and Y. He, "Imaging Functional and Structural Brain Connectomics in Attention-Deficit/Hyperactivity Disorder," *Molecular Neurobiology 2014 50:3*, vol. 50, no. 3, pp. 1111–1123, Apr. 2014. DOI: 10.1007/S12035-014-8685-X. [Online]. Available: https://link.springer.com/article/10.1007/s12035-014-8685-x.

[224] J. Posner, C. Park, and Z. Wang, "Connecting the Dots: A Review of Resting Connectivity MRI Studies in Attention-Deficit/Hyperactivity Disorder," *Neuropsychology Review 2014 24:1*, vol. 24, no. 1, pp. 3–15, Feb. 2014. DOI: 10.1007/S11065-014-9251-Z. [Online]. Available: https://link.springer.com/article/10.1007/s11065-014-9251-z.

[225] N. U. Dosenbach *et al.*, "Prediction of individual brain maturity using fMRI," *Science*, vol. 329, no. 5997, pp. 1358–1361, Sep. 2010. DOI: 10.1126/SCIENCE.1194144/SUPPL{_}FILE/DOSENBACH.SOM.REV1.PDF. [Online]. Available: https://www.science.org/doi/10.1126/science.1194144.

[226] D. A. Fair *et al.*, "Functional brain networks develop from a "local to distributed" organization," *PLoS Computational Biology*, 2009. DOI: 10.1371/journal.pcbi.1000381.

[227] K. Supekar, M. Musen, and V. Menon, "Development of Large-Scale Functional Brain Networks in Children," *PLOS Biology*, vol. 7, no. 7, e1000157, Jul. 2009. DOI: 10.1371/JOURNAL.PBIO.1000157. [Online]. Available: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000157.

[228] D. A. Fair *et al.*, "Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data," *Frontiers in Systems Neuroscience*, vol. 0, no. FEB, pp. 1–31, 2013. DOI: 10.3389/FNSYS.2012.00080/XML/NLM.

[229] G. S. Wig, "Segregated Systems of Human Brain Networks," *Trends in Cognitive Sciences*, vol. 21, no. 12, pp. 981–996, Dec. 2017. DOI: 10.1016/J.TICS.2017.09.006. [Online]. Available: http://www.cell.com/article/S1364661317301948/fulltext%20http://www.cell.com/article/S1364661317301948/abstract%20https://www.cell.com/trends/cognitive-sciences/abstract/S1364-6613(17)30194-8.

[230] T. D. Satterthwaite *et al.*, "Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth," *NeuroImage*, vol. 60, no. 1, pp. 623–632, Mar. 2012. DOI: 10.1016/J.NEUROIMAGE.2011.12.063.

[231] R. C. Oldfield, "The assessment and analysis of handedness: The Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, Mar. 1971. DOI: 10.1016/0028-3932(71)90067-4.

[232] D. Pappas, "ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation:" *http://dx.doi.org/10.1177/0734282905285792*, vol. 24, no. 2, pp. 172–178, Aug. 2016. DOI: 10.1177/0734282905285792. [Online]. Available: https://journals.sagepub.com/doi/abs/10.1177/0734282905285792?journalCode=jpaa.

[233] J. D. Power, B. L. Schlaggar, and S. E. Petersen, "Recent progress and outstanding issues in motion correction in resting state fMRI," *NeuroImage*, vol. 105, pp. 536–551, Jan. 2015. DOI: 10.1016/J.NEUROIMAGE.2014.10.044.

[234] S. M. Smith and T. E. Nichols, "Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference," *NeuroImage*, vol. 44, no. 1, pp. 83–98, Jan. 2009. DOI: 10.1016/J.NEUROIMAGE.2008.03.061.

[235] E. Y. Choi, B. T. Thomas Yeo, and R. L. Buckner, "The organization of the human striatum estimated by intrinsic functional connectivity," *Journal of Neurophysiology*, vol. 108, no. 8, pp. 2242–2263, Oct. 2012. DOI: 10.1152/JN.00270.2012/ASSET/IMAGES/LARGE/Z9K0191215870018.JPEG. [Online]. Available: https://journals.physiology.org/doi/10.1152/jn.00270.2012.

[236] D. C. Van Essen and D. L. Dierker, "Surface-Based and Probabilistic Atlases of Primate Cerebral Cortex," *Neuron*, vol. 56, no. 2, pp. 209–225, Oct. 2007. DOI: 10.1016/J.NEURON.2007.10.015. [Online]. Available: http://www.cell.com/article/S089662730700760X/fulltext%20http://www.cell.com/article/S089662730700760X/abstract%20https://www.cell.com/neuron/abstract/S0896-6273(07)00760-X.

[237] B. J. Casey *et al.*, "Implication of Right Frontostriatal Circuitry in Response Inhibition and Attention-Deficit/Hyperactivity Disorder," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 36, no. 3, pp. 374–383, Mar. 1997. DOI: 10.1097/00004583-199703000-00016.

[238] T. Sagvolden, E. B. Johansen, H. Aase, and V. A. Russell, "a dynamic developmental theory of attention-deficit/hyperactivity disorder (adhd) predominantly hyperactive/impulsive and combined subtypes," *Behavioral and Brain Sciences*, vol. 28, no. 3, pp. 397–419, Jun. 2005. DOI: 10.1017/S0140525X05000075. [Online]. Available: https://www.cambridge.org/core/journals/behavioral-and-brain-sciences/article/abs/dynamic-developmental-theory-of-attentiondeficithyperactivity-disorder-adhd-predominantly-hyperactiveimpulsive-and-combined-subtypes/8D2DCC90E03E6690ECBFBD85DCE99D66

[239] S. Cortese *et al.*, "Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI sudies," *American Journal of Psychiatry*, vol. 169, no. 10, pp. 1038–1055, Oct. 2012. DOI: 10.1176/APPI.AJP.2012.11101521/ASSET/IMAGES/LARGE/1038F3.JPEG. [Online]. Available: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2012.11101521.

[240] L. S. Hamilton *et al.*, "Reduced white matter integrity in attention-deficit hyperactivity disorder," *NeuroReport*, 2008. DOI: 10.1097/WNR.0b013e3283174415.

[241] L. M. Langevin, F. P. Macmaster, S. Crawford, C. Lebel, and D. Dewey, "Common white matter microstructure alterations in pediatric motor and attention disorders," *Journal of Pediatrics*, 2014. DOI: 10.1016/j.jpeds.2014.01.018.

[242] S. H. Mostofsky, K. L. Cooper, W. R. Kates, M. B. Denckla, and W. E. Kaufmann, "Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder," *Biological Psychiatry*, 2002. DOI: 10.1016/S0006-3223(02)01412-9.

[243] S. H. Mostofsky *et al.*, "Atypical motor and sensory cortex activation in attention-deficit/ hyperactivity disorder: A functional magnetic resonance imaging study of simple sequential finger tapping," *Biological Psychiatry*, 2006. DOI: 10.1016/j.biopsych.2005.06.011.

[244] L. An *et al.*, "Methylphenidate Normalizes Resting-State Brain Dysfunction in Boys With Attention Deficit Hyperactivity Disorder," *Neuropsychopharmacology 2013 38:7*, vol. 38, no. 7, pp. 1287–1295, Jan. 2013. DOI: 10.1038/npp.2013.27. [Online]. Available: https://www.nature.com/articles/npp201327.

[245] K. R. van Dijk, M. R. Sabuncu, and R. L. Buckner, "The influence of head motion on intrinsic functional connectivity MRI," *NeuroImage*, vol. 59, no. 1, pp. 431–438, Jan. 2012. DOI: 10.1016/J.NEUROIMAGE.2011.07.044.

[246] S. J. Kooij *et al.*, "European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD," *BMC Psychiatry*, 2010. DOI: 10.1186/1471-244X-10-67.

[247] J. C. Agnew-Blais, G. V. Polanczyk, A. Danese, J. Wertz, T. E. Moffitt, and L. Arseneault, "Evaluation of the persistence, remission, and emergence of Attention-deficit/hyperactivity disorder in young adulthood," *JAMA Psychiatry*, 2016. DOI: 10.1001/jamapsychiatry.2016.0465.

[248] G. J. DuPaul, "Parent and Teacher Ratings of ADHD Symptoms: Psychometric Properties in a Community-Based Sample," *Journal of Clinical Child Psychology*, 1991. DOI: 10.1207/s15374424jccp2003{_}3.

[249] M. Welvaert and Y. Rosseel, "On the definition of signal-to-noise ratio and contrast-to-noise ratio for fMRI data," *PLoS ONE*, vol. 8, no. 11, Nov. 2013. DOI: 10.1371/journal.pone.0077089.

[250] N. Makris *et al.*, "Anterior cingulate volumetric alterations in treatment-naïve adults with ADHD: A pilot study," *Journal of Attention Disorders*, 2010. DOI: 10.1177/1087054709351671.

[251] K. A. McKiernan, B. R. D'Angelo, J. N. Kaufman, and J. R. Binder, "Interrupting the "stream of consciousness": An fMRI investigation," *NeuroImage*, 2006. DOI: 10.1016/j.neuroimage.2005.09.030.

[252] M. F. Mason, M. I. Norton, J. D. Van Horn, D. M. Wegner, S. T. Grafton, and C. N. Macrae, "Wandering minds: The default network and stimulus-independent thought," *Science*, 2007. DOI: 10.1126/science.1131295.

[253] K. C. Fox, R. N. Spreng, M. Ellamil, J. R. Andrews-Hanna, and K. Christoff, *The wandering brain: Meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes*, 2015. DOI: 10.1016/j.neuroimage.2015.02.039.

[254] W. Li *et al.*, "Subregions of the human superior frontal gyrus and their connections," *NeuroImage*, 2013. DOI: 10.1016/j.neuroimage.2013.04.011.

[255] K. Jiang *et al.*, "Functional network connectivity changes in children with attention-deficit hyperactivity disorder: A resting-state fMRI study," *International Journal of Developmental Neuroscience*, vol. 78, no. 1, pp. 1–6, Nov. 2019. DOI: 10.1016/j.ijdevneu.2019.07.003. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1016/j.ijdevneu.2019.07.003.

[256] B. D. Mills *et al.*, "ADHD and attentional control: Impaired segregation of task positive and task negative brain networks," *Network Neuroscience*, 2018. DOI: 10.1162/netn{_}a{_}00034.

[257] Y. Fan, R. Wang, P. Lin, and Y. Wu, "Hierarchical integrated and segregated processing in the functional brain default mode network within attention-deficit/hyperactivity disorder," *PLoS ONE*, 2019. DOI: 10.1371/journal.pone.0222414.

[258] M. D. Greicius, K. Supekar, V. Menon, and R. F. Dougherty, "Resting-state functional connectivity reflects structural connectivity in the default mode network," *Cerebral Cortex*, 2009. DOI: 10.1093/cercor/bhn059.

[259] D. S. Margulies *et al.*, "Precuneus shares intrinsic functional architecture in humans and monkeys," *Proceedings of the National Academy of Sciences of the United States of America*, 2009. DOI: 10.1073/pnas.0905314106.

[260] R. Leech, S. Kamourieh, C. F. Beckmann, and D. J. Sharp, "Fractionating the default mode network: Distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control," *Journal of Neuroscience*, 2011. DOI: 10.1523/JNEUROSCI.5626-10.2011.

[261] C. Fassbender *et al.*, "A lack of default network suppression is linked to increased distractibility in ADHD," *Brain Research*, 2009. DOI: 10.1016/j.brainres.2009.02.070.

[262] M. Oldehinkel *et al.*, "Attention-Deficit/Hyperactivity Disorder Symptoms Coincide with Altered Striatal Connectivity," *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2016. DOI: 10.1016/j.bpsc.2016.03.008.

[263] W. Fries, "Cortical projections to the superior colliculus in the macaque monkey: A retrograde study using horseradish peroxidase," *Journal of Comparative Neurology*, 1984. DOI: 10.1002/cne.902300106.

[264] D. L. Gilbert, K. M. Isaacs, M. Augusta, L. K. MacNeil, and S. H. Mostofsky, "Motor cortex inhibition: A marker of ADHD behavior and motor development in children," *Neurology*, 2011. DOI: 10.1212/WNL.0b013e31820c2ebd.

[265] A. T. Mattfeld *et al.*, "Brain differences between persistent and remitted attention deficit hyperactivity disorder," *Brain*, 2014. DOI: 10.1093/brain/awu137.

[266] Y. Liu *et al.*, "Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: A review of resting-state fMRI studies," *Neuropsychologia*, 2008. DOI: 10.1016/j.neuropsychologia.2008.01.027.

[267] X. Long *et al.*, "Brain regional homogeneity and function connectivity in attenuated psychosis syndrome —based on a resting state fMRI study," *BMC Psychiatry*, 2018. DOI: 10.1186/s12888-018-1954-x.

[268] C. Tang, Y. Wei, J. Zhao, and J. Nie, "Different developmental pattern of brain activities in ADHD: A study of resting-state fMRI," *Developmental Neuroscience*, 2018. DOI: 10.1159/000490289.

[269] Z. Xu *et al.*, "Regional homogeneity and functional connectivity analysis of resting-state magnetic resonance in patients with bipolar II disorder," *Medicine (United States)*, 2019. DOI: 10.1097/MD.0000000000017962.

[270] L. Querne *et al.*, "Effects of Methylphenidate on Default-Mode Network/Task-Positive Network Synchronization in Children With ADHD," *Journal of Attention Disorders*, vol. 21, no. 14, pp. 1208–1220, Dec. 2017. DOI: 10.1177/1087054713517542. [Online]. Available: https://journals.sagepub.com/doi/10.1177/1087054713517542?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed.

[271] F. A. Picon *et al.*, "Methylphenidate Alters Functional Connectivity of Default Mode Network in Drug-Naive Male Adults With ADHD," *Journal of Attention Disorders*, vol. 24, no. 3, pp. 447–455, Feb. 2020. DOI: 10.1177/1087054718816822. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/30526190/.

[272] M. Wang, Z. Hu, L. Liu, H. Li, Q. Qian, and H. Niu, "Disrupted functional brain connectivity networks in children with attention-deficit/hyperactivity disorder: evidence from resting-state functional near-infrared spectroscopy," *Neurophotonics*, vol. 7, no. 01, p. 1, Mar. 2020. DOI: 10.1117/1.nph.7.1.015012.

[273] B. Sutcubasi, B. Metin, M. K. Kurban, Z. E. Metin, B. Beser, and E. Sonuga-Barke, *Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis*, Oct. 2020. DOI: 10.1080/15622975.2020.1775889.

[274] M. B. Jurado and M. Rosselli, *The elusive nature of executive functions: A review of our current understanding*, Sep. 2007. DOI: 10.1007/s11065-007-9040-z.

[275] V. Menon, "Salience Network," in *Brain Mapping: An Encyclopedic Reference*, vol. 2, Elsevier Inc., Feb. 2015, pp. 597–611. DOI: 10.1016/B978-0-12-397025-1.00052-X.

[276] S. M. Wolosin, M. E. Richardson, J. G. Hennessey, M. B. Denckla, and S. H. Mostofsky, "Abnormal cerebral cortex structure in children with ADHD," *Human Brain Mapping*, vol. 30, no. 1, pp. 175–184, Jan. 2009. DOI: 10.1002/hbm.20496.

[277] J. Ahrendts *et al.*, "Visual cortex abnormalities in adults with ADHD: A structural MRI study," *World Journal of Biological Psychiatry*, vol. 12, no. 4, pp. 260–270, Jun. 2011. DOI: 10.3109/15622975.2010.518624.

[278] E. Proal *et al.*, "Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood," *Archives of General Psychiatry*, vol. 68, no. 11, pp. 1122–1134, Nov. 2011. DOI: 10.1001/archgenpsychiatry.2011.117.

[279] T. Kolodny *et al.*, "Fronto-parietal engagement in response inhibition is inversely scaled with attention-deficit/hyperactivity disorder symptom severity," *NeuroImage: Clinical*, vol. 25, Jan. 2020. DOI: 10.1016/j.nicl.2019.102119.

[280] S. Gu *et al.*, "Emergence of system roles in normative neurodevelopment," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 44, pp. 13 681–13 686, Nov. 2015. DOI: 10.1073/pnas.1502829112.

[281] N. Leonardi *et al.*, "Principal components of functional connectivity: A new approach to study dynamic brain connectivity during rest," *NeuroImage*, vol. 83, pp. 937–950, Dec. 2013. DOI: 10.1016/j.neuroimage.2013.07.019.

[282] L. R. Chai *et al.*, "Evolution of brain network dynamics in neurodevelopment," *Network Neuroscience*, vol. 1, no. 1, pp. 14–30, 2017. DOI: 10.1162/NETN{_}a{_}00001.

[283] W. Lin *et al.*, "Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain," *American Journal of Neuroradiology*, vol. 29, no. 10, pp. 1883–1889, Nov. 2008. DOI: 10.3174/ajnr.A1256.

[284] H. M. de Bie *et al.*, "Resting-state networks in awake five- to eight-year old children," *Human Brain Mapping*, vol. 33, no. 5, pp. 1189–1201, May 2012. DOI: 10.1002/hbm.21280.

[285] J. R. Sato *et al.*, "Age effects on the default mode and control networks in typically developing children," *Journal of Psychiatric Research*, vol. 58, pp. 89–95, Nov. 2014. DOI: 10.1016/j.jpsychires.2014.07.004.

[286] K. Rebello, L. M. Moura, W. H. Pinaya, L. A. Rohde, and J. R. Sato, *Default Mode Network Maturation and Environmental Adversities During Childhood*, 2018. DOI: 10.1177/2470547018808295.

[287] B. J. Harrison *et al.*, "Dynamic Subcortical Modulators of Human Default Mode Network Function," *Cerebral Cortex*, Dec. 2021. DOI: 10.1093/cercor/bhab487.

[288] F. Katsuki and C. Constantinidis, *Bottom-up and top-down attention: Different processes and overlapping neural systems*, Oct. 2014. DOI: 10.1177/1073858413514136.

[289] L. Tucha *et al.*, "Sustained attention in adult ADHD: time-on-task effects of various measures of attention," *Journal of Neural Transmission*, vol. 124, pp. 39–53, Feb. 2017. DOI: 10.1007/s00702-015-1426-0.

[290] S. H. Mostofsky and D. J. Simmonds, "Response inhibition and response selection: Two sides of the same coin," *Journal of Cognitive Neuroscience*, vol. 20, no. 5, pp. 751–761, May 2008. DOI: 10.1162/JOCN.2008.20500. [Online]. Available: /record/2008-04571-001.

[291] S. M. Ravizza and C. S. Carter, "Shifting set about task switching: Behavioral and neural evidence for distinct forms of cognitive flexibility," *Neuropsychologia*, vol. 46, no. 12, pp. 2924–2935, Oct. 2008. DOI: 10.1016/j.neuropsychologia.2008.06.006.

[292] H. B. Halleland, J. Haavik, and A. J. Lundervold, "Set-shifting in adults with ADHD," *Journal of the International Neuropsychological Society*, vol. 18, no. 4, pp. 728–737, 2012. DOI: 10.1017/S1355617712000355.

[293] L. N. Irwin, M. J. Kofler, E. F. Soto, and N. B. Groves, "Do children with attention-deficit/hyperactivity disorder (adhd) have set shifting deficits?" *Neuropsychology*, vol. 33, no. 4, pp. 470–481, May 2019. DOI: 10.1037/neu0000546.

[294] D. Keltner and J. S. Lerner, "Emotion," in *Handbook of Social Psychology*, Hoboken, NJ, USA: John Wiley & Sons, Inc., Jun. 2010. DOI: 10.1002/9780470561119.socpsy001009.

[295] S. Koole, *The psychology of emotion regulation: An integrative review*, 2009. DOI: 10.1080/02699930802619031.

[296] A. Stringaris and R. Goodman, "Mood lability and psychopathology in youth," *Psychological Medicine*, vol. 39, no. 8, pp. 1237–1245, Aug. 2009. DOI: 10.1017/S0033291708004662.

[297] K. R. Overgaard *et al.*, "Continuity in features of anxiety and attention deficit/hyperactivity disorder in young preschool children," *European Child and Adolescent Psychiatry*, vol. 23, no. 9, pp. 743–752, Sep. 2014. DOI: 10.1007/s00787-014-0538-7.

[298] R. A. Barkley and M. Fischer, "The Unique Contribution of Emotional Impulsiveness to Impairment in Major Life Activities in Hyperactive Children as Adults," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 49, no. 5, pp. 503–513, May 2010. DOI: 10.1016/j.jaac.2010.01.019.

[299] G. W. Leibniz, *Monadology (1714)*. [Online]. Available: https://philpapers.org/rec/LEIM-3.

APPENDICES

Appendix 1. DSM-V Diagnostic Criteria for Attention Deficit and Hyperactivity Disorder

Diagnostic Criteria

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
   c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
   h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
   i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   a. Often fidgets with or taps hands or feet or squirms in seat.
   b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
   c. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
   d. Often unable to play or engage in leisure activities quietly.
   e. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
   f. Often talks excessively.
   g. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
   h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
   i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

314.01 (F90.2) Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

314.00 (F90.0) Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

314.01 (F90.1) Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

Appendix 2. Cognitive and emotional processes

- **Attention**:Attention is a cognitive process that controls and manages the resources of the mind. Since there is a huge amount of inner and outer stimuli and a limited amount of computational resources it is necessary to select where we are directing these resources to [288]. That is what attention does, and it can be divided in three different functions: bottom-up attention or salience is an automatic process that focuses our mind to a "salient" stimulus (e.g. an strident noise), top-down attention is the voluntary focus on certain stimulus, and sustained attention keeps the focus on a stimulus or a task for a continuous time. These different functions also involve different brain areas, as displayed in Figure 11. Sustained attention is the main attentional process altered in ADHD [289], however, these results must be interpreted with care since deficits in other cognitive processes such as working memory or motivation may be the cause of it.

- **Response Inhibition**: It is a cognitive process that suppresses actions that are inappropriate or unwanted for achieving a goal [290]. According to Barkley, response inhibition consists in three interrelated processes: inhibiting a prepotent response (a response that results in immediate reinforcement), stopping an ongoing response, and suppressing the response to salient stimuli for keeping focus [87]. Response inhibition has been proposed as the core deficit in ADHD, affecting other domains such as working memory or sustained attention [87], but there is now controversy about this hypothesis [15, 88].

- **Working Memory**: Working memory is one of the three types of memory, being the other two short-term memory and long-term memory. While these two latter types of memory functions are only differentiated by the amount of time that the information is retained, working memory refers to the information that is handled "online". We can see it as the RAM (Random Access Memory) of a computer, which is the information that it is manipulating at a determined moment. There are several articles reporting deficits in working memory in ADHD, and concretely spatial working memory seems to be more affected than verbal working memory [83, 84]. However, various cognitive processes are involved in the tasks used for measuring working memory (such as attention or motivation), so special care is required when interpreting the results of these studies.

- **Set Shifting**: Set shifting is a process that refers to the ability to change the attentional set, defining set as the properties of the stimulus that are relevant [291]. One of the most notable examples of set-shifting is the figure-ground perceptual grouping used in Gestalt (Figure 1). This cognitive function is related to attention and specially to response inhibition in that it is necessary to inhibit certain stimuli to focus on others. There are studies showing moderate effect size impairment of set-shifting ability in both children [88] and adults [292] with ADHD, although

other studies suggest that if response inhibition is executed successfully there is no evidence of alteration of set-shifting alone [293].

- **Motivation**: Motivation is a wide construct that describes a variety of functions, but in summary it is the mechanism that engages the subject into goal-directed action [90]. It is related to reward because normally motivational action requires perceiving potential value on the outcome of the behavior. There is a great amount of evidence of impaired motivation and reward perception in ADHD, making people with the disorder more prone to initiate actions with an immediate reward even if it is much smaller than the long-term one [11, 12]. However, even if reward and motivation are tightly related they are not the same construct and more studies that aim to clearly differentiate alterations in these two functions are needed [90].

- **Emotional Regulation**: Although intuitive and even obvious from an everyday-life perspective, the consensual definition of emotion is hard to find. For the sake of simplicity, we will define it as Lazarus, who states that "Emotions are organized psychophysiological reactions to news about ongoing relationships with the environment" (Lazarus, 1991; more information on this debate can be found elsewhere [294]). Emotional regulation, thus, is people's ability to redirect their emotional status and resist being carried away by their psychophysiological outcomes [295]. Emotional dysregulation (lack of emotional regulation) has been consistently reported in ADHD across all lifespan [296, 297], and even if this symptom is present in a wide variety of mental disorders its presence in ADHD cannot be explained by comorbidity [298].

Appendix 3. Philosophical foundations of Systems and Network Analysis

Network Analysis is based on the philosophical theory of relation, which states that the properties of the substances are based on their relationships with other substances instead. The roots of this framework lie in the works of Gottfried Leibniz, specially his Monadology [299]. This author claimed that the world is constituted of indivisible closed elements called monads, similar to what was the primal definition of atoms. However (and this is where the difference with atoms lies), the monads are not substantial elements but infinitesimal units of analysis, that is, they are conceptual elements that depend on the scale of observation. For example, if we are analyzing a social network, each person can be a monad because it is indeed the infinitesimal unit of analysis at that scale. Another example could be found if we examine an ecological system, where the living beings would be the monads. In the case of the brain, depending on which resolution we are studying we can define different elements as indivisible. For example in experiments with a small nervous tissue we could use the neurons as monads, but in fMRI we could use the voxels (which are going to represent a group of neurons) or even regions of the brain.

In Leibniz's words "all the monads express each other because they all represent the same universe under their particular point of view" [299], which means that each of them is defined by their relation (point of view) with the rest of them. Again, in the case of rfMRI data, a voxel would be defined by its FC with the rest of the voxels of the brain, which is its particular "point of view" of the system. That is why the Monadology represents a definition of holism as the unity in multiplicity, namely, that the multiple units and their interactions between them constitute a unitary element, which is a network or in mathematical terms, a graph.