SFU SURJ | SIMON FRASER UNIVERSITY SCIENCE UNDERGRADUATE RESEARCH JOURNAL
Vol. 4 (2018-19)

A Review of Altered Neurophysiology and Connectivity of the Brain in Autism Spectrum Disorder and its Impact on Common Symptoms

Payman Baharmand[1]*
Sam Doesburg[2]

[1]Simon Fraser University, *Faculty of Health Science*
[2]Simon Fraser University, *Department of Biomedical Physiology & Kinesiology*

Abstract

Autism Spectrum Disorder (ASD) is a developmental condition which refers to a broad range of abnormalities and challenges with social skills, cognitive abilities, and behaviour. The prevalence of ASD is increasing, yet we currently do not have a clear neurodevelopmental understanding of this complex disorder. A narrative review is done on the topic of abnormal functional connectivity in ASD and its relation to some of the symptoms and consequences which have been observed in the literature. Thus, no formal process was used to carry out this review and no attempt was made to conduct a statistical analysis of the data. The purpose of this review is to integrate the findings related to the topic in a meaningful and logical manner. The review will also discuss related topics such as white matter connectivity, anatomical and pathological findings, in addition to biochemical changes observed in the ASD brain. Findings from studies discussed such features and changes in the ASD brain using different brain imaging methods. A review of the literature guides us to the conclusion that there is no single causal gene or exclusive physiological factor for ASD. Furthermore, we find that there is also no universal case of under- or overconnectivity in autistic brains. Instead, we observe variation in abnormal connectivity between different brain areas, which are theorized to be associated with some of the commonly reported symptoms in ASD.

Keywords — Autism Spectrum Disorder, Neurodevelopment, Neuroatypical, Functional Connectivity, Structural Connectivity, Neuroanatomy, Neurophysiology, Neurochemical, fMRI, EEG, MEG

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition which is characterized by difficulties in social communication and repetitive and/or restricted behaviours and/or interests. Over the years, research has allowed for advancements in reasonably accurate diagnosis. One popular diagnostic technique is the Autism Diagnostic Observation Schedule (ADOS), which is an assessment of communication and social behaviour for individuals who may potentially have ASD or

*Corresponding Author: payman.b.baharmand@gmail.com

other pervasive psychological and neurodevelopmental disorders. The test involves the administration of standardized activities organized into four modules, based on the participant's age and language development. The examiner would then observe the presence or absence of key behaviours associated with ASD and formulate a score used to make a diagnosis [1]. This is just one example of several other diagnostic techniques which clinicians and researchers may find helpful, yet there is still a large gap in finding clear biomarkers that would ideally provide more reliable and valid diagnoses. A biomarker is any objective indicator that could be accurately and reproducibly measured to determine the medical status of an individual [2]. Autistic individuals do not present any particular physical appearances; unlike other developmental disorders, such as Down Syndrome and Cornelia de Lange Syndrome. On the other hand, autistic individuals have been shown to share relatively subtle distinct facial features which have only been reported in males [3]. A recent study by Tan and colleagues [4] found that increased facial masculinity in ASD correlated with greater communication difficulties based on the ADOS. Indeed, genetic and epigenetic factors could also serve as biomarkers for diseases and illness. Individuals can have a genetic predisposition to ASD [5, 6, 7]. However, there is a high volume of candidate genes which may be involved [6] which by definition makes ASD a polygenic condition. Furthermore, this introduces another dimension of complexity and results in ASD to not have a clear genetic basis or any obvious biomarker(s) that would be easily associated.

More interestingly, ASD subjects have a wide spectrum of different complications and characteristics, yet there are unifying symptoms which are hallmarks of the condition, such as impaired communication and social behaviour, restricted range of interests, and repetitive behaviour [8]. ASD is often diagnosed after infancy and its occurrence is reported in all racial, ethnic, and socioeconomic groups, where delays in diagnosis were found in certain cultural groups [9, 10]. The prevalence of ASD is greater in males as indicated by a study which found that males were four times more likely than females to be diagnosed with the condition [11]. There is an increasing prevalence of ASD, but we have yet to identify a clear pathophysiologic basis of the condition. Research to fill this gap has shown promising findings and has led to many paths for further and much-needed investigations.

A useful theory to provide some foundational explanation to the mechanism of ASD and its associated symptoms is studying the functional connectivity of the autistic brain. Functional connectivity of the brain refers to the synchronization of activity between different areas of the brain. In other words, this parameter qualitatively indicates how collaboration occurs between different cortical regions and structures, and how much of it is taking place. This idea links neurophysiological information, obtained through brain imaging modalities, and histological findings with behavioural observations. Thus, it can serve as an effective path to have a better understanding of the disorder. Researchers from different branches of neuroscience and psychology, as well as the engineering sciences, have been led to discover that there seem to be distortions in functional connectivity for subjects diagnosed with ASD, compared to their neurotypical (NT) counterparts [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22].

A battery of psychological tasks have been used to test and measure participants' cognitive and motor performance, all while using brain imaging modalities such as

functional magnetic resonance imaging (fMRI) [23, 24, 12, 25, 13, 26, 27, 14, 15, 28, 16, 29, 30, 31], magnetoencephalography (MEG) [32], and electroencephalography (EEG) [33] to collect data pertaining to cortical activity, primarily, but not limited to, functional connectivity. Authors also make use of complex computational models and cognitive architectures [34, 17] to connect their results with theories about how the brain systematically operates. Other forms of data which some authors point to include histological [35, 36, 37, 38], structural connectivity [24, 27, 18, 39], anatomical [40, 41, 42, 43, 44, 45], and biochemical abnormalities [46, 47] observed in ASD. In this narrative literature review, we will discuss some of these studies and their findings with a greater emphasis on the role of functional connectivity in several of the most common complications seen in ASD. The rationale for this review paper is to provide readers with insights about the biomedical findings of ASD with an emphasis on neurophysiological findings.

2. Functional Imaging Results

The neurobiology of ASD is being extensively studied to find some notable evidence for differences in functional and structural connectivity between the brains of individuals with ASD versus NT controls [48]. One of the earliest suggestions directs our attention to fMRI results which support the claim that there is reduced long-distance connectivity between the frontal and posterior regions in the autistic brain [12, 25, 13, 26, 15]. This influential idea is known as the underconnectivity theory of autism. In their review article, Just and colleagues [34] refer to numerous fMRI studies which show such reduced inter-regional communication as mentioned above in ASD participants during several cognitive tasks. The fMRI studies show impaired activation and synchronization in the frontal and posterior regions, which can be linked to the observed decrease in performance in a wide range of cognitive tasks such as language comprehension [25], executive functioning [12], social processing [28, 29, 49], working memory [15, 28], advanced inhibition [26, 30]. and visuospatial processing [23]. Just [34] suggests that poor capabilities with these cognitive tasks, especially those involving Theory of Mind and executive functioning, serve as evidence for the theory of underconnectivity in the frontal lobe of the cerebral cortex due to the great demand of that specific region for carrying out these tasks.

Furthermore, a computational model was used to demonstrate what the functional connectivity would look like in individuals with ASD under an executive functioning task known as the Tower of London. The computational model showed supporting results for the underconnectivity theory, and moreover, Just and colleagues [34] elaborated on two concluding cases. Firstly, the authors concluded that there is constrained "communication bandwidth" [34] between the frontal and posterior regions of the cortex, where communication bandwidth is described by the authors as the optimal rate of information transfer along a neural path. Secondly, this difficulty with proper communication leads to the need for the parietal area to function without central input from the frontal area to complete a given task. Thus, this will lead to the adaptation of having a greater parietal autonomy. This is considered by the authors as a more comprehensive theoretical model of the autistic brain and its implication in the decreased functional

connectivity as noted above. Nevertheless, there is increasing evidence hinting that there is more to discover, as other studies exhibit cases of both underconnectivity and overconnectivity (hypoconnectivity and hyperconnectivity, respectively) [19].

A study by Redcay and colleagues [16] looked at whole-brain functional connectivity in NT adolescents and ones with ASD, aged 14 to 20 years, using graph theory and resting-state functional connectivity magnetic resonance imaging (fcMRI). They observed increased functional connectivity between the right lateral parietal region and prefrontal regions in the ASD group. Building upon this, Delmonte and colleagues [18] found abnormally high functional connectivity of frontostriatal connections in adolescents with ASD. In terms of the default mode network, decreased connectivity was reported between anterior and posterior default mode sub-networks in adolescents with ASD [31]. Local overconnectivity in posterior occipital and temporal areas in addition to local underconnectivity in posterior cingulate and medial prefrontal regions were found in adolescents with ASD, using a voxel-based approach to measure functional connectivity between a particular voxel and its nearest neighbours [14]. It is important to note that fcMRI studies show diverse findings in connectivity with respect to specific regions and different states, such as resting state versus task state, measured in participants [48]. This variation in under- and overconnectivity patterns across different regions of the cortex is expected since there is strong evidence that the autistic brain does show structural and functional differences compared to a typically developing brain.

Functional connectivity may also change depending on age; thus, the study of differences in this phenomenon through a developmental aspect deserves adequate attention. Uddin and colleagues [20] present evidence which exhibits overall overconnectivity in the brains of younger children afflicted with ASD. Another study utilized functional near-infrared spectroscopy to look at the same topic but specifically looked at infants at one year of age who were not diagnosed with ASD but were a high-risk group for the disorder. As early as three months into their life, these selected infants showed overall overconnectivity compared to the control group, but this difference was no longer present in the later months to follow [21]. More recent evidence found that high risk infants showing abnormal connectivity at six months of age were more likely to be diagnosed with ASD and show greater symptom severity, such as repetitive behaviour and restricted social-communication skills [50, 51, 52].

3. Structural Imaging Results

Functional connectivity can also be better understood by investigating the structural or anatomical connectivity of the brain. Diffusion tensor imaging (DTI) is an effective way to accomplish this. Specifically, DTI can be implemented to study white matter tracts and their connectivity [48]. White matter is of special interest due to its broad and vital role in supporting neurons, particularly in neural communication within the cortex and periphery. Making a link between functional and structural connectivity may be difficult, as illustrated by Delmonte and colleagues [18], whose study was mentioned above for reporting overconnectivity between the striatum and frontal cortex during the resting state. However, they were unable to find evidence for differences

in structural connectivity of the frontostriatal tracts via DTI. The authors suggest that the observed overconnectivity may be due to functional reorganization in the autistic brain instead of an anatomical abnormality. On the other hand, one cannot ignore other anatomical deviations in the autistic brain, and their potential role in atypical functional connectivity. Cortical connectivity in adults with ASD was found to be affected by intracranial volume [39]. The authors believe there is a possibility that this consequence of constrained long-range connectivity is manifested by the early brain overgrowth in ASD. A significant relationship was found between abnormal white matter structure and distortions in functional connectivity during the completion of a visuospatial task [27]. Using fMRI and high angular diffusion MRI, the change was more notably recorded in the connections between the left occipital lobe and five regions in the left hemisphere. An influential study by Deshpande and colleagues [24] used fMRI and theory of mind task to make some interesting findings regarding connectivity differences in ASD. Up to 19 cortical pathways were found to be reliable in distinguishing participants with ASD from those who were NT. These cortical pathways were found to be altered in the autistic group in terms of effective connectivity. Effective connectivity is the direct influence of one brain area over another [48]. The difference in effective connectivity between the two groups was prominent enough to allow a 95% accuracy rate in predicting experimental participants from controls. Aside from its remarkably high accuracy with predicting effective connectivity, one can appreciate the authors' choice to use three complementary metrics: functional connectivity, white matter connectivity, and effective connectivity.

4. Biochemical Findings

The neurochemistry of the brain can be non-invasively studied in vivo through proton magnetic resonance spectroscopy (1H MRS) or also commonly known as nuclear magnetic resonance (NMR) spectroscopy. Using similar principles as MRI, this analytical approach has been used to study the concentration of brain metabolites as biomarkers for various neurological and psychiatric conditions, such as ASD [46, 47].

Friedman and colleagues [46] used an advanced form of 1H MRS, known as proton echo-planar spectroscopic imaging (PEPSI), where the relative concentrations of selected chemicals could be obtained from multiple brain regions all at once, rather than having to do it repetitively for each of the single three dimensional spaces in the brain (ie. a single voxel approach). The goal of the study was to quantitatively measure and analyze the concentrations of N-acetylaspartate (NAA), creatine plus phosphocreatine (Cre), choline (Cho), and myoinositol (mI) in addition to relaxation times of 45 children from the ages of 3 to 4 years [46]. The participants were children with ASD, NT, or had some form of delayed neurodevelopment. The authors found a decrease in NAA, Cre, Cho, and mI concentrations for the ASD group, compared to the NT subjects in several brain regions such as the cingulate gyrus, white matter tracts associated with the corpus callosum as well as the frontal and parietal lobes, gray matter associated with the temporal lobe, and subcortical structures such as the thalamus and the insula. These reductions in NAA, Cre, Cho, and mI concentrations for the ASD group were reported to be subtle, such that it would not support their hypothesis of increased neuronal

density in ASD and its role in faulty apoptosis (cell death) or synaptic pruning. However, it is important to note the role NAA has in the synthesis of lipid by oligodendrocytes, the glial cells that provide myelination for the axons of neurons in the central nervous system (CNS) [53]. Thus, this observed chemical imbalance may be implicated in the abnormal functional connectivity reported in ASD; especially in the cases of the underconnectivity reported in the frontal and parietal regions [12, 25, 13, 26, 15] with regard to the reductions of NAA in the white matter tracts of the frontal and parietal lobe [46]. Levitt and colleagues [47] conducted a similar study using 1H MRS and MRI, but in a single voxel approach, for several brain regions and subcortical structures. They included 22 children with ASD, who were in an older and broader age range (5 to 16 years of age) and had 20 age-matched NT controls. Comparing the ASD subjects with the NT controls, there was no significant difference in NAA concentrations, but significant differences were found in Cho concentrations [47], which is contrary to Friedman's findings. Cho levels were found to be reduced by 27.2% in ASD subjects in the inferior anterior cingulate and increased by 19.1% in the right caudate nucleus [47]. Cre levels were increased in the right caudate nucleus by 21% but also reduced by 17.9% in the body of the left caudate nucleus and right occipital cortex [47], which is consistent with Friedman's findings. With that said, Levitt did observe relatively larger reductions in Cre [47]. In summary, the authors were able to show that differences in metabolites exist between ASD and control subjects.

5. Pathological Findings

It is now widely accepted that ASD is a multifactorial disorder [54], meaning that ASD is dependent on various genetic and environmental factors. As with most multifactorial health complications, there are several genes which are involved in susceptibility and resistance to the development of ASD, in addition to significant influence by environmental factors [54]. Furthermore, ASD primarily involves the brain and increased brain size is the most prevalent trait regarding abnormal cortical structure [54]. This brain overgrowth does not result in damage to subcortical structures and spaces. This phenomenon is not specific to a certain brain area, although some authors have found the most significant increase to be in the frontal lobe [41, 43]. Some cases involve overgrowth in the cerebellum as well [40, 45] but increased size of the cortex seems to be supported more soundly [44]. More interestingly, white matter volume has been shown to be disproportionately larger in ASD subjects [38]. Casanova and colleagues [42] attribute this to the distortions in the structure and number of minicolumns which would have an impact on their circuitry. Minicolumns are organizational units consisting of layers of connected neurons arranged in vertical columns which cumulatively comprise the cortex, especially the superior area of the brain responsible for higher cognitive functioning which is known as the neocortex.

A comprehensive review by Goldberg and colleagues [55] argues that most of the neuroimaging findings of increased brain size may not be reliable since these experiments have not been replicated and do not make a proper effort to control extraneous variables. In terms of increased cerebral size, the author suggests that overgrowth in the temporoparietal region is the only appropriately replicated finding,

rather than enlargement of the frontal region, which is more frequently reported [55].

So far, no definite conclusions have been drawn about a cellular pathological feature in ASD. However, postmortem histological studies have shown atypical differences in the minicolumns of autistic brains [36, 37]. One of the most consistent changes in morphometry is the decreased width of minicolumns. This finding was verified by Buxhoeveden and colleagues [35] in another experiment involving a quantitative technique, known as Gray Level Index (GLI), to analyze stained tissues from postmortem ASD samples. GLI is the ratio of the area covered by stained cell bodies to those that are not stained. The initial analysis carried out by the authors was measuring the peaks of stained gray matter areas to find the column width. Other modifications of the GLI method [37] all led to the same result of a reduced minicolumn width, in addition to an increase in the number of minicolumns and a decrease in the size of neurons [5, 36]. Given the hypothesized importance of these minicolumns in the development and organization of the neocortex and white matter [36], it is no surprise that abnormal brain growth would be seen in ASD. These columns of pyramidal neurons are connected to each other through regional and global white matter tracts, such as those in the corpus callosum [54]. Reduction in the width of minicolumns and the size of their constituting neurons will be accompanied by an increase in the number of columns, which is linked to an increase in local and global neural fibre projections [56]. The former is more commonly observed because long white matter tracts are more physically and metabolically taxing [54]. However, by favouring shorter local projections, short-range functional connectivity is enhanced while long-range functional connectivity is not [54]. This would then direct back to the findings of decreased frontal and posterior connectivity as previously mentioned above [12, 25, 13, 26, 15]. Therefore, a distorted minicolumnar hypothesis may have an integral role in the changes in regional and long-range functional connectivity in ASD.

6. Discussion

There are an increasing number of studies being done on ASD participants who are on the high functioning end of the spectrum. Although the recent discoveries in ASD research are exciting, they also raise the concern of a bias towards high-functioning individuals within the ASD population, therefore inevitably neglecting research on the more severe or low functioning autistic individuals.

The approach of incorporating two or more neuroimaging techniques is key for this domain of research. Each tool has its advantages and drawbacks over the other. MRI experiments, which are done in various forms, are highly popular and some may argue that they are the most prolific, but they are also in fact very costly [16]. MRI techniques used in this field of research allow excellent spatial resolution but poor temporal resolution. However, EEG and MEG provide a different window of studying functional connectivity through having a high temporal resolution and moderate spatial resolution. Moreover, they are also not affected by motion artifacts which can introduce errors in connectivity measurements taken in fcMRI experiments [48]. With that said, EEG data was used to support the claim of both underconnectivity and overconnectivity in ASD [33], and interestingly, MEG results also led to observing different abnormalities

in brain oscillations in ASD samples and their family members who share half of their genome [32].

Genetic and cellular studies may lead to promising discoveries regarding atypical functional connectivity in ASD, but such studies face many obstacles such as difficulty with in-vivo cellular experiments with ASD participants, ethical issues since the syndrome is only found in humans and the demand for large sample sizes needed for completing meaningful genomic studies. Ultimately, the future of ASD research holds much potential in terms of experiments which involve a combination of different imaging approaches. Additionally, future studies should continue to consider analyzing more than one connectivity or physiological index as this approach can lead to more fruitful findings regarding the neurodevelopment of ASD and its link to reported symptoms and reliable biomarkers.

7. Conclusion

Investigating the literature makes it very clear that ASD exemplifies a complex neurodevelopmental disorder with a neurological and genetic basis that manifests itself in diverse psychological and physical symptoms and complications. One overarching topic is the distortions that have been reported in functional connectivity. Similar to our understanding that there is no single causal gene or environmental factor for ASD, we find that there is also no single region in the cerebrum where under- or overconnectivity is shown in individuals with ASD. Rather, there seems to be a mixture of atypical connectivity between different brain regions which can be associated with some common ASD symptoms. For instance, the observed frontal underconnectivity may be associated with deficits in executive functioning and language learning [28, 34, 49]. Mixed patterns of underconnectivity with the frontal area and overconnectivity in the cerebellum [22] may be related to even less frequent symptoms such as altered motor behaviour and coordination. Functional connectivity can also be used to account for the advantages observed in some cases of ASD. For instance, considering the important role posterior areas have in perceptual learning and processing [16, 34], one can note the consistency between improved perceptual functioning in ASD with the findings of overconnectivity in posterior regions, namely the temporal, parietal, and occipital areas, in addition to the proposed theory of greater parietal autonomy [14, 34].

8. Acknowledgments

At this time, I wish to express my sincere gratitude to my primary supervisor, Dr. Sam Doesburg, for the constant support and invaluable input as I completed my first semester of Directed Studies. Additionally, I wish to acknowledge the graduate students of the lab: Evan Hutcheon, Nataliia Kozhemiako, and Adonay Nunes, for addressing any questions I had and directing me to the appropriate resources when needed. Last but certainly not least, I wish to thank Dr. Mark Lechner, the Director of Undergraduate Programs at SFU's Faculty of Health Sciences, for his instrumental cooperation with the approval of this project on behalf of the Faculty of Health Sciences. This journey would not have been possible without the incredibly compassionate and

intelligent people acknowledged above.

References

[1] Autism Genetic Resource Exchange (AGRE). About the ados*. URL https://research.agre.org/program/aboutados.cfm.

[2] Kyle Strimbu and Jorge A Tavel. What are biomarkers? *Current Opinion in HIV and AIDS*, 5(6):463, 2010.

[3] Kristina Aldridge, Ian D George, Kimberly K Cole, Jordan R Austin, T Nicole Takahashi, Ye Duan, and Judith H Miles. Facial phenotypes in subgroups of prepubertal boys with autism spectrum disorders are correlated with clinical phenotypes. *Molecular Autism*, 2(1):15, 2011.

[4] Diana Weiting Tan, Syed Zulqarnain Gilani, Murray T Maybery, Ajmal Mian, Anna Hunt, Mark Walters, and Andrew JO Whitehouse. Hypermasculinised facial morphology in boys and girls with autism spectrum disorder and its association with symptomatology. *Scientific reports*, 7(1):9348, 2017.

[5] Manuel F Casanova. Neuropathological and genetic findings in autism: the significance of a putative minicolumnopathy. *The Neuroscientist*, 12(5):435–441, 2006.

[6] Judith H Miles. Autism spectrum disorders-a genetics review. *Genetics in Medicine*, 13(4):278, 2011.

[7] Stéphane Jamain, Hélène Quach, Catalina Betancur, Maria Råstam, Catherine Colineaux, I Carina Gillberg, Henrik Soderstrom, Bruno Giros, Marion Leboyer, Christopher Gillberg, et al. Mutations of the x-linked genes encoding neuroligins nlgn3 and nlgn4 are associated with autism. *Nature genetics*, 34(1):27, 2003.

[8] American Psychiatric Association et al. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub, 2013.

[9] Maureen S Durkin, Matthew J Maenner, F John Meaney, Susan E Levy, Carolyn DiGuiseppi, Joyce S Nicholas, Russell S Kirby, Jennifer A Pinto-Martin, and Laura A Schieve. Socioeconomic inequality in the prevalence of autism spectrum disorder: evidence from a us cross-sectional study. *PloS one*, 5(7):e11551, 2010.

[10] Maureen S Durkin, Matthew J Maenner, Jon Baio, Deborah Christensen, Julie Daniels, Robert Fitzgerald, Pamela Imm, Li-Ching Lee, Laura A Schieve, Kim Van Naarden Braun, et al. Autism spectrum disorder among us children (2002–2010): socioeconomic, racial, and ethnic disparities. *American journal of public health*, 107 (11):1818–1826, 2017.

[11] Deborah L Christensen, Kim Van Naarden Braun, Jon Baio, Deborah Bilder, Jane Charles, John N Constantino, Julie Daniels, Maureen S Durkin, Robert T Fitzgerald, Margaret Kurzius-Spencer, et al. Prevalence and characteristics of autism spectrum

disorder among children aged 8 years–autism and developmental disabilities monitoring network, 11 sites, united states, 2012. *MMWR Surveillance Summaries*, 65(13):1, 2018.

[12] Marcel Adam Just, Vladimir L Cherkassky, Timothy A Keller, Rajesh K Kana, and Nancy J Minshew. Functional and anatomical cortical underconnectivity in autism: evidence from an fmri study of an executive function task and corpus callosum morphometry. *Cerebral cortex*, 17(4):951–961, 2006.

[13] Rajesh K Kana, Timothy A Keller, Vladimir L Cherkassky, Nancy J Minshew, and Marcel Adam Just. Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. *Brain*, 129(9):2484–2493, 2006.

[14] Jose Omar Maximo, Christopher L Keown, Aarti Nair, and Ralph-Axel Müller. Approaches to local connectivity in autism using resting state functional connectivity mri. *Frontiers in human neuroscience*, 7:605, 2013.

[15] Hideya Koshino, Patricia A Carpenter, Nancy J Minshew, Vladimir L Cherkassky, Timothy A Keller, and Marcel Adam Just. Functional connectivity in an fmri working memory task in high-functioning autism. *Neuroimage*, 24(3):810–821, 2005.

[16] Elizabeth Redcay, Joseph M Moran, Penelope Lee Mavros, Helen Tager-Flusberg, John DE Gabrieli, and Susan Whitfield-Gabrieli. Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder. *Frontiers in human neuroscience*, 7:573, 2013.

[17] Vassilis Tsiaras, Panagiotis G Simos, Roozbeh Rezaie, Bhavin R Sheth, Eleftherios Garyfallidis, Eduardo M Castillo, and Andrew C Papanicolaou. Extracting biomarkers of autism from meg resting-state functional connectivity networks. *Computers in biology and medicine*, 41(12):1166–1177, 2011.

[18] Sonja Delmonte, Louise Gallagher, Erik O'hanlon, Jane Mc Grath, and Joshua H Balsters. Functional and structural connectivity of frontostriatal circuitry in autism spectrum disorder. *Frontiers in human neuroscience*, 7:430, 2013.

[19] Ralph-Axel Müller, Patricia Shih, Brandon Keehn, Janae R. Deyoe, Kelly M. Leyden, and Dinesh K. Shukla. Underconnected, but How? A Survey of Functional Connectivity MRI Studies in Autism Spectrum Disorders. *Cerebral Cortex*, 21(10): 2233–2243, 03 2011. ISSN 1047-3211.

[20] Lucina Uddin, Kaustubh Supekar, and Vinod Menon. Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Frontiers in Human Neuroscience*, 7:458, 2013. ISSN 1662-5161.

[21] Brandon Keehn, Jennifer Wagner, Helen Tager-Flusberg, and Charles Nelson. Functional connectivity in the first year of life in infants at-risk for autism: a preliminary near-infrared spectroscopy study. *Frontiers in Human Neuroscience*, 7: 444, 2013. ISSN 1662-5161.

[22] Sylvain Baillet. Magnetoencephalography for brain electrophysiology and imaging. *Nature Neuroscience*, 20:327 EP –, Feb 2017. Review Article.

[23] Saudamini Roy Damarla, Timothy A Keller, Rajesh K Kana, Vladimir L Cherkassky, Diane L Williams, Nancy J Minshew, and Marcel Adam Just. Cortical underconnectivity coupled with preserved visuospatial cognition in autism: Evidence from an fmri study of an embedded figures task. *Autism Research*, 3(5):273–279, 2010.

[24] Gopikrishna Deshpande, Lauren Libero, Karthik Ramakrishnan Sreenivasan, Hrishikesh Deshpande, and Rajesh Kumar Kana. Identification of neural connectivity signatures of autism using machine learning. *Frontiers in human neuroscience*, 7:670, 2013.

[25] Marcel Adam Just, Vladimir L Cherkassky, Timothy A Keller, and Nancy J Minshew. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain*, 127(8):1811–1821, 2004.

[26] Rajesh K Kana, Timothy A Keller, Nancy J Minshew, and Marcel Adam Just. Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. *Biological psychiatry*, 62(3):198–206, 2007.

[27] Jane McGrath, Katherine Johnson, Erik O'Hanlon, Hugh Garavan, Louise Gallagher, and Alexander Leemans. White matter and visuospatial processing in autism: a constrained spherical deconvolution tractography study. *Autism Research*, 6(5):307–319, 2013.

[28] Hideya Koshino, Rajesh K Kana, Timothy A Keller, Vladimir L Cherkassky, Nancy J Minshew, and Marcel Adam Just. fmri investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. *Cerebral cortex*, 18(2):289–300, 2007.

[29] Sarah E Schipul, Diane L Williams, Timothy A Keller, Nancy J Minshew, and Marcel Adam Just. Distinctive neural processes during learning in autism. *Cerebral cortex*, 22(4):937–950, 2011.

[30] Marjorie Solomon, Sally J Ozonoff, Stefan Ursu, Susan Ravizza, Neil Cummings, Stanford Ly, and Cameron S Carter. The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia*, 47(12):2515–2526, 2009.

[31] Tuomo Starck, Juha Nikkinen, Jukka Rahko, Jukka Remes, Tuula Hurtig, Helena Haapsamo, Katja Jussila, Sanna Kuusikko-Gauffin, Marja-Leena Mattila, Eira Jansson-Verkasalo, et al. Resting state fmri reveals a default mode dissociation between retrosplenial and medial prefrontal subnetworks in asd despite motion scrubbing. *Frontiers in human neuroscience*, 7:802, 2013.

[32] Isabelle Buard, Sally J Rogers, Susan Hepburn, Eugene Kronberg, and Donald Rojas. Altered oscillation patterns and connectivity during picture naming in autism. *Frontiers in Human Neuroscience*, 7:742, 2013.

[33] Robert Coben, Iman Mohammad-Rezazadeh, and Rex Lee Cannon. Using quantitative and analytic eeg methods in the understanding of connectivity in autism spectrum disorders: a theory of mixed over-and under-connectivity. *Frontiers in human neuroscience*, 8:45, 2014.

[34] Marcel Adam Just, Timothy A Keller, Vicente L Malave, Rajesh K Kana, and Sashank Varma. Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. *Neuroscience & Biobehavioral Reviews*, 36(4):1292–1313, 2012.

[35] Daniel P Buxhoeveden, Andrew E Switala, Emil Roy, and Manuel F Casanova. Quantitative analysis of cell columns in the cerebral cortex. *Journal of neuroscience methods*, 97(1):7–17, 2000.

[36] Manuel F Casanova, Daniel P Buxhoeveden, Andrew E Switala, and Emil Roy. Minicolumnar pathology in autism. *Neurology*, 58(3):428–432, 2002.

[37] MF Casanova, I Van Kooten, AE Switala, H Van Engeland, H Heinsen, HWM Steinbusch, PR Hof, and C Schmitz. Abnormalities of cortical minicolumnar organization in the prefrontal lobes of autistic patients. *Clinical Neuroscience Research*, 6(3-4):127–133, 2006.

[38] MR Herbert, DA Ziegler, CK Deutsch, LM O'brien, N Lange, A Bakardjiev, J Hodgson, KT Adrien, S Steele, N Makris, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. *Brain*, 126(5):1182–1192, 2003.

[39] John D Lewis, Rebecca Theilmann, Jeanne Townsend, and Alan Evans. Network efficiency in autism spectrum disorder and its relation to brain overgrowth. *Frontiers in human neuroscience*, 7:845, 2013.

[40] Eric Courchesne, CM Karns, HR Davis, R Ziccardi, RA Carper, ZD Tigue, HJ Chisum, P Moses, K Pierce, C Lord, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an mri study. *Neurology*, 57(2):245–254, 2001.

[41] Ruth A Carper, Pamela Moses, Zachary D Tigue, and Eric Courchesne. Cerebral lobes in autism: early hyperplasia and abnormal age effects. *Neuroimage*, 16(4): 1038–1051, 2002.

[42] Manuel F Casanova. White matter volume increase and minicolumns in autism. *Annals of neurology*, 56(3):453–453, 2004.

[43] Martha R. Herbert, David A. Ziegler, Nikos Makris, Pauline A. Filipek, Thomas L. Kemper, Joseph J. Normandin, Heather A. Sanders, David N. Kennedy, and Verne S. Caviness Jr. Localization of white matter volume increase in autism and developmental language disorder. *Annals of Neurology*, 55(4):530–540, 2004.

[44] Joseph Piven, Eileen Nehme, Jon Simon, Patrick Barta, Godfrey Pearlson, and Susan E. Folstein. Magnetic resonance imaging in autism: measurement of the cerebellum, pons, and fourth ventricle. *Biological Psychiatry*, 31(5):491 – 504, 1992. ISSN 0006-3223.

[45] B. F. Sparks, S. D. Friedman, D. W. Shaw, E. H. Aylward, D. Echelard, A. A. Artru, K. R. Maravilla, J. N. Giedd, J. Munson, G. Dawson, and S. R. Dager. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*, 59(2):184–192, 2002. ISSN 0028-3878.

[46] S.D. Friedman, D.W. Shaw, A.A. Artru, T.L. Richards, J. Gardner, G. Dawson, S. Posse, and S.R. Dager. Regional brain chemical alterations in young children with autism spectrum disorder. *Neurology*, 60(1):100–107, 2003.

[47] Jennifer G Levitt, Joseph O'Neill, Rebecca E Blanton, Susan Smalley, David Fadale, James T McCracken, Donald Guthrie, Arthur W Toga, and Jeffrey R Alger. Proton magnetic resonance spectroscopic imaging of the brain in childhood autism. *Biological Psychiatry*, 54(12):1355 – 1366, 2003. ISSN 0006-3223.

[48] Rajesh K. Kana, Lucina Q. Uddin, Tal Kenet, Diane Chugani, and Ralph-Axel Müller. Brain connectivity in autism. *Frontiers in Human Neuroscience*, 8:349, 2014. ISSN 1662-5161.

[49] Rajesh K. Kana, Timothy A. Keller, Vladimir L. Cherkassky, Nancy J. Minshew, and Marcel Adam Just. Atypical frontal-posterior synchronization of theory of mind regions in autism during mental state attribution. *Social Neuroscience*, 4(2): 135–152, 2009.

[50] Robert W. Emerson, Chloe Adams, Tomoyuki Nishino, Heather Cody Hazlett, Jason J. Wolff, Lonnie Zwaigenbaum, John N. Constantino, Mark D. Shen, Meghan R. Swanson, Jed T. Elison, Sridhar Kandala, Annette M. Estes, Kelly N. Botteron, Louis Collins, Stephen R. Dager, Alan C. Evans, Guido Gerig, Hongbin Gu, Robert C. McKinstry, Sarah Paterson, Robert T. Schultz, Martin Styner, , Bradley L. Schlaggar, John R. Pruett, and Joseph Piven. Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age. *Science Translational Medicine*, 9(393), 2017. ISSN 1946-6234.

[51] Christian O'Reilly, John D. Lewis, and Mayada Elsabbagh. Is functional brain connectivity atypical in autism? a systematic review of eeg and meg studies. *PLOS ONE*, 12(5):1–28, 05 2017.

[52] Rianne Haartsen, Emily J. H. Jones, Elena V. Orekhova, Tony Charman, Mark H. Johnson, S. Baron-Cohen, R. Bedford, A. Blasi, P. Bolton, S. Chandler, C. Cheung, K. Davies, M. Elsabbagh, J. Fernandes, I. Gammer, H. Garwood, T. Gliga, J. Guiraud, K. Hudry, M. Liew, S. Lloyd-Fox, H. Maris, L. O'Hara, G. Pasco, A. Pickles, H. Ribeiro, E. Salomone, L. Tucker, A. Volein, and The BASIS team. Functional eeg connectivity in infants associates with later restricted and repetitive behaviours in autism; a replication study. *Translational Psychiatry*, 9(1):66, 2019. ISSN 2158-3188.

[53] Morris H Baslow. Functions of n-acetyl-l-aspartate and n-acetyl-l-aspartylglutamate in the vertebrate brain. *Journal of Neurochemistry*, 75(2):453–459, 2000.

[54] Manuel F. Casanova. *The Neuropathology of Autism*, chapter 21. American Cancer Society, 2014. ISBN 9781118911389.

[55] Jeremy Goldberg, Peter Szatmari, and Claude Nahmias. Imaging of autism: Lessons from the past to guide studies in the future. *The Canadian Journal of Psychiatry*, 44(8):793–801, 1999.

[56] Michel A Hofman. Brain evolution in hominids: are we at the end of the road. *Evolutionary anatomy of the primate cerebral cortex*, pages 113–127, 2001.

[57] Aarthi Padmanabhan, Andrew Lynn, William Foran, Beatriz Luna, and Kirsten O'Hearn. Age related changes in striatal resting state functional connectivity in autism. *Frontiers in Human Neuroscience*, 7:814, 2013. ISSN 1662-5161.

[58] Ingmar Blümcke, Maria Thom, Eleonora Aronica, Dawna D. Armstrong, Harry V. Vinters, Andre Palmini, Thomas S. Jacques, Giuliano Avanzini, A. James Barkovich, Giorgio Battaglia, Albert Becker, Carlos Cepeda, Fernando Cendes, Nadia Colombo, Peter Crino, J. Helen Cross, Olivier Delalande, François Dubeau, John Duncan, Renzo Guerrini, Philippe Kahane, Gary Mathern, Imad Najm, Çiğdem Özkara, Charles Raybaud, Alfonso Represa, Steven N. Roper, Noriko Salamon, Andreas Schulze-Bonhage, Laura Tassi, Annamaria Vezzani, and Roberto Spreafico. The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc task force of the ilae diagnostic methods commission1. *Epilepsia*, 52(1):158–174, 2011.

[59] Peter B. Crino. mtor signaling in epilepsy: Insights from malformations of cortical development. *Cold Spring Harbor Perspectives in Medicine*, 5(4), 2015.

[60] Steven J Luck. *An introduction to the event-related potential technique*. MIT press, 2014.