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The Amsterdam University College (AUC) Undergraduate Journal of Liberal Arts and Sciences is an interdisciplinary publication showcasing outstanding undergraduate academic papers. The Journal aims to demonstrate the strength of undergraduate scholarship at AUC, to reflect the intellectual diversity of its academic programme, to encourage best research and writing practices, to facilitate collaboration between students and faculty across the curriculum, and to provide students with opportunities to gain experience in academic reviewing, editing, and publishing. The Editorial staff of the Journal is composed of members of the InPrint board, a registered AUCSA committee.

Foreword by Dr. Antonio Luchicchi
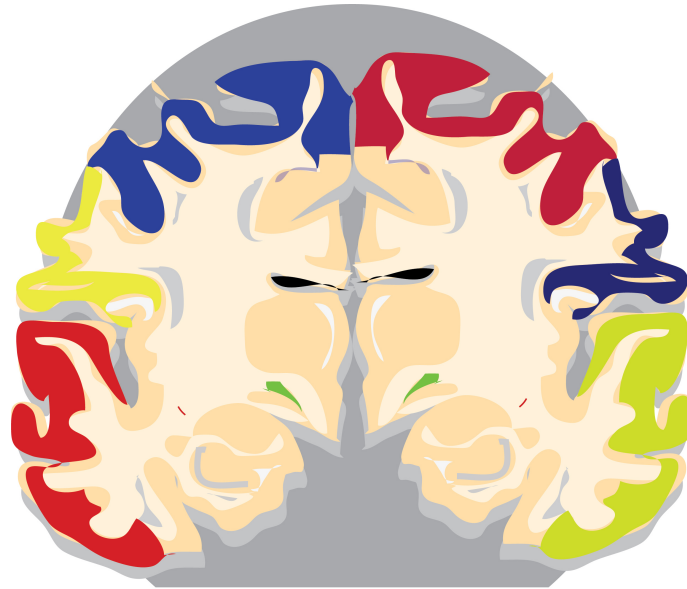
The progress of science is a necessary step forward to guarantee the development of human beings. In neuroscience, finding new approaches and solutions to the current problems is even more important as the brain, the imperator of the central nervous system, is as noble as immensely complex. At the state of the art we only understand a little part of it, and many more mysteries and secrets are jealously held in this apparently inexpugnable box made of roughly 100 billion of neural cells.

Students are our hope. Their new and fresh look at old problems can be the way to find more suitable solutions for the progress of neuroscience. As assistant professor, I have the fortune to teach for 60% of my time. This time is 100% devoted to discussing with brilliant students about the past, present, and future of the neuroscientific discipline. This pleasure and honor has brought me to let the audience hear the voice and the opinion of the young minds with whom I have the fortune to grow as a lecturer.

Therefore, I asked them to write an editorial in which they would freely express their opinion about a current problem in the neuroscientific field and envision a way to fix it in the coming 20 years. In response to this request, I received a number of great manuscripts whose focus ranged from the development of more sensitive tools to explore normality and pathology of the nervous system to the incorporation of important societal aspects in the neuroscientific discussion.

This special issue of AUC's *Undergraduate Journal of Liberal Arts and Sciences* proposes a selection of the most impressive papers the students of my Neuroscience course have produced. In the following pages, themes including the role of artificial intelligence in understanding the brain complexity, the importance of an individual treatment for neurodegenerative disorders, and the weight of sex differences in neuropharmacology will be treated. In my opinion, all these manuscripts express the essence of what a new generation of professionals must be: "rational dreamers," experts able to look at the world with the fascination of a child and analyze the phenomena with the instruments of a mature scientist.

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Foreword

It is our honor and privilege to introduce this Special Issue of Amsterdam University College's (AUC) Undergraduate Journal of Liberal Arts and Sciences.

For this Issue, we collaborated with Dr. Antonio Luchicchi, compiling the most promising papers from the Neuroscience course. While many exist within the well-defined scientific body of knowledge delineated by a textbook, it is the remarkable few that push the boundaries of science, embracing the constant transformation that shatters paradigms. It is our belief that these papers spark constructive discourse and thus humbly present an Issue with papers that each may, in their own right, help change the way we approach neuroscience and the world. The Issue begins with Marta Sokół's inspiring proposal to enlist the help of artificial intelligence in understanding the human brain. Following that, Maxence-Viktor Liesenborgs offers a fresh perspective of the possible biomarkers of neurodegenerative diseases, involving the gut-brain axis. Finally, Shany Aflalo presents a critical introspection of sex differences in neuroscience research that has, within the history of neuroscience, placed an emphasis on males for their research.

The interdisciplinary nature of this Special Issue demanded a wide range of editors. Naturally, this Issue would not have been possible without the fervent commitment of the editors and authors, whose belief in the work was matched by their enthusiasm for the collaboration. Furthermore, special thanks go to DIVCom, the Diversity Commission of AUC, who collaborated with us to ensure we maintained inclusive rhetoric in our publication. We would also like to give thanks to Dr. Antonio Luchicchi who proposed this Special Issue, and his indubitable belief in the future of scholarship.

It is our sincere hope that this Issue will inspire you to think beyond the comfort of the curriculum and venture into the rewarding freedom of unbridled inquiry, perhaps even contributing to future Issues.

Aditi Rai Sia, Editor-in-Chief &
Aada Kallio, Managing Editor and Head of Sciences

Contents

Improvise, Adapt, Overcome:

Using Artificial Intelligence to Surpass the Limitations of Organic Intelligence in Understanding the Complexity of the Brain

Marta Sokół

Introduction

One of the main challenges of neuroscience is its seemingly unimaginable complexity. In contrast to other natural sciences, neuroscience is vastly interdisciplinary, encompassing not only biological, but also cognitive, behavioral, and emotional data. Ironically, this complexity oftentimes makes studying the human brain an overwhelming task for the human brain. In this paper, I postulate that for neuroscientific research to make progress in the next 20 years, limitations of the human mind in studying the brain must be overcome by the use of artificial intelligence (AI). Although the introduction of AI may yield numerous possible avenues of development within the discipline, I propose in this essay three major areas of progress which should be pursued. First, I argue that models based on deep learning may improve the understanding of the connection between cognition and the brain. Second, machine learning should become more frequently used in prospective diagnostics of neurodegenerative diseases to make healthcare more efficient. Finally, in-silico labeling should be investigated as a possible, non-invasive method of labeling live neurons. Altogether, I believe that making progress in these areas of AI will likely be the impetus for the development of approaches to neuroscience surpassing the capabilities of organic human intelligence.

Deep Learning

The first of the aforementioned methods – deep learning – can be used to create neuroscientific models that imitate neural responses of the brain, known as neural networks. While neural networks were first constructed more than six decades ago, they had not initially been used for neuroscientific inquiry (Widrow & Hoff, 1960). Only fairly recently have reliable models of neural activity in the brain cortices been modeled. In one such pioneering study, the activity of the ventral visual pathway, responsible for visual recognition of objects, was accurately modeled, imitating both the inferior temporal cortex and in one of the visual areas, V4 (Yamins et al., 2014). It was achieved with the use of a method known as performance optimization, which identified a neural network matching human performance on a range of recognition tasks, even when the input data was extrapolated outside neural data. Since these promising results suggest that deep learning-based models may quantitatively imitate neural processing in the cerebral cortex, more models were constructed to mimic the activity of sensory cortices (Yamins & DiCarlo, 2016).

It seems likely that even more functionally complex cognitive processes can also be modeled, suggesting that in the future, it will be possible to model not only the human brain but also the human mind mathematically. While in colloquial language the difference between the brain and the mind seems vague, in scientific jargon the former concept refers to concrete biological structures underlying mental processes, whereas the latter relates to these processes themselves. In general, although it is easy to envision the pure physicality of the brain, operationalizing the mind remains challenging. However, one recent promising research using AI-based methods showed that understanding communication and cognition may soon be within our reach (Papadimitriou et al., 2020). In the study, a model imitating the activity of neuronal assemblies, called the Assembly Calculus, which is a computational system capable of capturing cognitive phenomena including language or memory, had been constructed. A subsequent study raised the hypothesis that mimicking the brain's ability to learn is possible (Dabagia et al., 2021). Although the study is currently undergoing a peer review stage, it preliminarily shows that the constructed model is capable of associating classes, otherwise known as assemblies, with responses to concrete stimuli, which may then be recalled. Based on these findings, this model may reliably imitate the learning and memorizing capabilities of the brain due to its ability to infer knowledge from limited data without requiring external supervision. As one of the first models to mimic human cognition reliably, it unravels the possibility that this recent avenue of research may play a major role in improving our understanding of the association between cognition and the brain. Therefore, the pursuit of modeling these interactions via computational methods may lead to considerable developments in the domain of cognitive neuroscience and, hence, should become a topic of interest within the discipline.

Machine Learning

Secondly, machine learning could potentially serve as an early screening method prior to the onset of a neurodegenerative disease (Myszczynska et al., 2020). This is relevant as the symptoms of numerous neurodegenerative diseases are currently detectable only after significant neuropathological damage has occurred (Donev et al., 2009; Michel et al., 2016). However, machine learning models are capable of recognizing potential early, pre-onset signs of impairment based on large datasets, such as health records, thereby serving as an ideal tool for such purposes. For instance, it would theoretically be possible to screen individual patients for markers of common aging-related diseases, which could then form a compound score of blood test results, cognitive performance testing, or results on any other indicators. Although such a solution has not yet been tested on patients, it would ensure a more accurate, personalized approach to diagnosing medical conditions, which due to the sheer amount of data could not be provided by healthcare specialists. Apart from drawing diagnostic inferences from big data, machine learning can also be used in interpreting neuroimaging data (Erickson et al., 2017), which could become part of the datasets used in early screenings for neurodegeneration in the future. The benefits of using machine learning in automated pre-onset, nationwide screening programs could presumably include lessening the burden on the healthcare workers, and highly increasing the efficiency and lowering the costs of diagnosis with a minimal need for supervision. These potential advantages would not only be limited to this aspect, as the introduction of machine learning would also train the algorithms on large datasets to pinpoint neurodegenerative markers prior to onset, which when identified, could improve the understanding of a given neuropathological disease.

Machine learning in pre-onset screenings for neurodegenerative diseases is currently being employed in some pilot pre-clinical research, although it has not yet been introduced into wide, nation-level use despite the potential benefits it could bring. Due to this fact, it can be argued that the use of machine learning in neurological pre-onset diagnostics could serve as a quick and accurate pre-onset diagnostic tool. Fortunately, considering the historical trajectories of the interplay be-

tween the disciplines of neurodiagnostic and AI-based methods, this development may soon be introduced into common medical use. Namely, expert systems first started to be utilized in neuropathological diagnosis under the supervision of a human specialist (deFigueiredo et al., 1995), relying on experience provided by neuroradiologists (Wang et al., 2016). At first, computer-aided diagnosis was frequently used in research, characterized by quantitative analysis of clinically important characteristics of neuropathology (e.g., measurement of the thickness of the cerebral cortex), with the ultimate diagnosis being made by a human professional (Maldjian et al., 2003). While computer-aided diagnosis surpasses the human diagnostic capabilities with its fast, accurate, and unbiased quantitative measurements of any given structures of interest, supervised learning techniques also began to be used in identification of less observable neuropathological hallmarks from MRI or CT data, allowing for a predictive diagnosis of Alzheimer's disease (Gray et al., 2013; Korolev et al., 2017) or cognitive decline (Choi et al., 2018). Finally, preliminary reports suggest that the combination of both MRI imaging data and cognitive assessment scores could be an efficient and early prospective diagnostic tool (Lundervold & Lundervold, 2019), characterized by low failure rates and quick processing time (Myszczynska et al., 2020). Therefore, it may be capable of accurately detecting the progression from a mild cognitive impairment to Alzheimer's disease (Davatzikos et al., 2008; Fan et al., 2008). In short, the introduction of machine learning in pre-onset screenings of large populations for neurodegenerative diseases could be used reliably, and it should gain importance in the near future. This would not only have positive consequences for the efficiency and costs of healthcare, but also for the current understanding of the early origins of neurodegeneration; since the knowledge learned by machine learning-based algorithms could possibly identify new early markers of neuropathology, which are undetectable to the human eye.

Labeling Neurons

Finally, the use of AI in neuroscience in the next 20 years should become more ubiquitous in the domain of histology, since studying neurons consti-

tutes is perhaps one of the greatest challenges of this discipline. Although across the decades, numerous methods of labeling neurons have been devised, the majority of them can neither use live cells (e.g., Nissl and Golgi staining), add multiple labels, nor stain neurons selectively (e.g., DiO and DiI; Honig et al., 1989; Kádár et al., 2009). Additionally, labeling neurons with fluorescence-based techniques requires induction of changes in gene expression, which might have an impact on protein functioning (Sariyer, 2013). Therefore, it seems essential to find another labeling method devoid of these limitations, to develop neuroscience in the near future.

A good candidate for such an alternative is a machine learning-based labeling method, known as "in-silico labeling" (ISL; Christiansen et al., 2018). ISL has been shown to accurately predict fluorescent labels of unlabeled live or fixed samples contained in microscopy images, determining the cell type and state, as well as nuclei labels. Although this neural network was constructed for a wide variety of cells, originating from different tissues, it could prove to be particularly useful in labeling neurons due to the fact that single neurons assemble into complex networks. Indeed, ISL was found to differentiate neurons from astrocytes and immature cells in culture, and determine whether a given structure was a dendrite or an axon. Furthermore, these in-silico labels were shown to be as reliable as true labels, predicted by the researchers, which was reflected in a similar number of detected inconsistencies in classification. However, although the authors of the study have successfully shown that ISL can be used as a non-invasive, accurate method of labeling live cells, these findings have not been investigated further in neurons. Therefore, in the near future, it ought to be determined whether deep neural networks could be capable of envisioning inappreciable information in either live or fixed cells, as this could not only have critical consequences, such as more efficient and approachable labeling of live neurons, but it could also be possible that other, previously uncapturable mechanisms could be envisioned with the use of machine learning.

Conclusion

To conclude, this paper stresses the importance of increasing the use of AI in various branches of neuroscience. The need to focus on investigating neuroscientific problems with AI is reflected in recent dynamic developments in numerous specific subdomains of the discipline, reflecting the potential upcoming and ubiquitous role of computational models and automation in the next 20 years. While still in the early phases of development, some of the most important new areas of improvement include: deep learning models based on deep learning to mimic neural foundations of human cognition; the use of machine learning in prospective screenings for neurodegenerative diseases in large populations; and in-silico, non-invasive labeling of live neurons. In short, the use of AI not only seems to be an essential development in neuroscience, but given its potential presence in a wide variety of different aspects of the discipline, it will likely become the major avenue of the development of neuroscience in the next 20 years. It is now our time to reconcile with the fact that in order to study the human brain accurately, one must abandon organic intelligence for the sake of artificial intelligence.

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The Gut-Brain Axis as a Possible Biomarker For Neurodegenerative Diseases

An Avenue for Personalized Medicine

Maxence-Viktor Liesenborgs

Introduction

Modern medicine is mostly 'one-size-fits-all' for patients; for treatment of a certain disease, the same type of medications are prescribed to everyone. Unfortunately, not every patient exhibiting the same disease will respond to the same customs of treatment. The Leukemia Lymphoma Society describes this phenomenon as a tailor making clothes for someone from a picture without knowing the actual measurements (1). Similar to the tailor, medical specialists find it difficult to create something to fit the individual, rather, individuals are given a one-size-fits-all option off the rack. Personalized medicine attempts to rectify this by tailoring the course of treatment to each individual based on their genetics, environment, and pathophysiological status (2). The alternative course of treatment often uses genome sequencing, physiological, hemodynamic, and neuroimaging investigations to explore the diagnosis and treatment of several diseases. These may include Parkinson's disease (PD), Alzheimer's disease (AD), cancers, depressive disorders, and multiple sclerosis. To highlight the significance of this research, in 2020 in the United States of America alone, neurodegenerative diseases cost the economy $655 billion (3). These huge costs reflect the prevalence of neurodegenerative diseases and dementia, which have an incidence of 17.2 million people per year, a number that has been progressively increasing (4). As the burden of these diseases on the patients, family members, health care staff, and the economy is so high, it is unfortunate that the best treatments for PD and AD aim to simply slow down disease progression or help alleviate symptoms, without hopes for a cure (5). For this editorial, the focus will lie in neurodegenerative diseases such as PD and AD, and explore the gut-brain axis as a biomarker for them, which may give insight into personalized treatment approaches.

Examining Neurodegenerative Diseases, the Gut, and the Microbiome: Gut-Brain Axis

Neurodegenerative diseases have been linked to the gut-brain axis, which works as follows: the enteric nervous system (ENS) innervates two intramuscular plexuses that line the gut and consist of neurons and glial cells (6). The ENS also controls multiple gut functions and, for this reason, can be regarded as the nervous system of the gut. The gut-brain axis comprises the ENS, vagus nerve, and immune system, which allows bidirectional communication between the brain and gut (5). Similarly, the gut microbiome has multiple functions that contribute to this bidirectional communication by means of synthesizing bio- and neuroactive metabolites and neurotransmitters. Therefore, the gut-brain axis has an influence on behavior, cognition, mood, and the development of the brain, alongside psychological, psychiatric, and neurodegenerative diseases. However, the gut microbiota also plays a role in pathology, as it can produce harmful metabolites that create inflammation in the gut, the enteric nervous system, and the central nervous system, as well as an increase in the permeability of the intestinal and the blood-brain barriers (5). Through the increased permeability, the harmful metabolites can leak into the systemic circulation and reach the brain, thereby contributing to the development of neurodegenerative diseases. The incidence is especially increased for people who are older, may have vascular deficits, or both (5).

As neurodegenerative diseases, the loss of structure and function in the brain is central to both PD and AD. On the one hand, PD is marked by a loss of dopamine neurons in the brain, usually in the substantia nigra, a dopaminergic nucleus in the midbrain that is part of the basal ganglia and has a role in movement and reward (7). The typical symptoms associated with PD are bradykinesia, resting tremor, postural instability (motor dysfunction), depression, sleep disturbances, and cognitive decline (non-motor features) (8). On the other hand, AD is known for the buildup of amyloid plaques[1] and neurofibrillary tangles[2] in the brain, and it is characterized with a progression to dementia and increasing cognitive impairment (8,9). Controversially, hypotheses have said that PD may begin in the gut, not the brain, and that a dysbiosis in the gut microbiome can possibly trigger its progression. These hypotheses are supported by evidence that the gastrointestinal problems that accompany

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[1]Amyloid plaques consist of misfolded β-amyloid peptides, and the plaques disrupt cell function.

[2]Neurofibrillary tangles are aggregates of hyperphosphorylated tau protein. The tangles can interfere with synaptic communication and contribute to neurodegeneration.

PD present themselves in advance to the neurological complications (5). Moreover, a study shows that the microbiome in patients with PD is altered to a great degree in composition and function (10). Therefore, the enteric nervous system has usually already been subjected to nerve degeneration before the classical symptoms of PD arise, which also makes assessing the prevalence of the disease difficult (11). Similarly, patients with AD also show an altered composition in the gut microbiome (8). Likewise, some gut microbes (i.e., *Escherichia coli*) are able to produce amyloids and in this manner contribute to amyloid plaques, which partially makes AD a metabolic disease (5). A study demonstrated that the gut microbiota regulates neuroinflammation, and an alteration in its composition would favor motor dysfunction in PD and β-amyloid deposition in AD (4), which is in line with the aforementioned. From the studies presented, it is apparent that the gut is implicated in the progression of both PD and AD, and the gut-brain axis is undeniably involved. Together, these findings highlight the need for research on the link between the brain, the gut, and the gut microbiome.

Biomarker for Parkinson's Disease and Alzheimer's Disease

A lack of treatments to prevent the diseases is due to the absence of a biomarker that would allow for early diagnosis, indicating that the pathology of the diseases is already too far advanced at the time of diagnosis such that intervention is not possible. In 2017, a review discussed the link between the gut-brain axis and neurodegenerative diseases in animal models (12). Then, in 2021, a study in South Korea investigated this relationship by observing more than 100 000 patients with inflammatory bowel disease (IBD) or without (control group) (8). Although patients from both groups (with and without IBD) had developed a neurodegenerative disease (PD or AD), they concluded that the group of patients with IBD had a higher chance of developing a neurodegenerative disease. These findings highlight the role of the gut in the pathology of neurodegenerative diseases. However, this might not be the only factor at play. For example, age is another factor that has already been correlated. Therefore, there could be several elements that contribute to a higher occurrence of PD

and AD. The more factors of neurodegenerative diseases revealed, the more elucidated the diseases become, the easier it is to treat them and prevent them, thereby lowering the burden of these diseases on the patient and the economy.

Standardizing Gut Microbiome Analysis Tools for Personalised Medicine

In the next 20 years, there are several ways we can move towards solidifying a metabolic biomarker for PD and AD, of which two will be clarified in the following. First, it is crucial to note that we need to normalize looking at symptoms as being cooperative rather than as separate entities that should be treated individually. "The Mind-Gut Connection" by Emeran Mayer expresses that physicians in many instances refused to acknowledge the importance of the patient's symptoms of abnormal gut reactions if an endoscopy did not reveal a severe malady (i.e., gut inflammation or a tumor) (11). Instead, Mayer points out, they are more likely to suggest special diets, probiotics, or pills, without searching for the true cause of the symptoms (11). Thus, the lack of standardized techniques to examine the gut microbiome prevents further knowledge and interferes with patients finding the underlying conditions (i.e., neurodegenerative diseases) that may originate in the gut and are causing them to display an array of symptoms.

This leads to the second point: techniques to map the gut microbiome that already exist today need to be further evolved and standardized. Though, before delving into the techniques used to map the gut microbiome, it is important to state that factors, such as age, sex, ethnicity, and lifestyle (diet, exercise, and medication), can influence the composition of the gut (5). Metagenomics uses an array of genomic technologies and bioinformatics tools in order to elucidate the genetic content of the gut microbiome composition. Unfortunately, this does not measure the activity of the gut population. To find the activity, scientists use metatranscriptomics, metaproteomics, and metabolomics (5). Metatranscriptomics can isolate mRNA from individual microbes within fecal samples, which is then sequenced to reveal the genes that are expressed by the microbiome community, the transcriptome (5). A metapro-

teomic analysis uses mass spectrometry to measure the proteins expressed by the microbiome, the proteome. To measure metabolic concentration, metabolomics is used, and it can directly read current concentrations in a biofluid, tissue, or cell (5). In order to develop these techniques further, they must be first incorporated into standard practice. The more these analyses are used, the faster scientists will be able to detect what we are missing and what needs to be fixed with the tools. Therefore, by standardizing and developing these techniques as diagnostic tools, they can be included in routine check-ups at the doctor to augment patient care.

Conclusion

To recapitulate, there is a need to break away from the 'one-size-fits-all' medicine for neurodegenerative diseases. The onset of the diseases happens differently, varying from person to person. Although the disease in some people might develop due to age, on other occasions, it can be due to an altered gut microbiome. While there is little we can do in the former case, early diagnostics and interference in the latter may have wide implications for personalized treatments of the diseases. One way we can start is to tailor routine check-ups at the doctor to each patient, trying to connect the symptoms and incorporating tests (i.e., metagenomics, metatranscriptomics, metaproteomics, and metabolomics) into standard practice. This way, if neurodegenerative diseases are caught early, the cost to the economy also diminishes. Nonetheless, the end goal is to have discovered a metabolic biomarker for PD and AD through personalized medicine in the next 20 years.

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Sex Matters in Neuropharmacology

Where Are We Now and What Future Directions Should Be Taken?

Shany Aflalo

Preface

In this paper, the term sex refers to sex assigned at birth and is distinct from inquiry relating to gender. It is important to acknowledge that there are many other aspects of sex that fall through the cracks in neuropharmacology research, for example, people undergoing hormone replacement therapy. This paper aims to highlight the importance of the inclusion of the female sex in neuropharmacology research, which is just one of the many aspects in the field that requires advancement.

Introduction

There are more females in our population, more females with chronic diseases, and more females visiting physicians than males (Franconi et al., 2007). Yet, clinical and neuroscientific research has predominantly considered the male sex to suffice as the best representative of the human species (Franconi et al., 2007). As the different sexes display variabilities in symptomatology in different disorders, this assumption is flawed. For example, the prevalence and symptoms of neuropsychiatric disorders, such as major depressive disorder (MDD), differ between the sexes (Fernández-Guasti et al., 2012). This is also the case for the neurobiological mechanisms, prevalence, and severity of MDD (Fernández-Guasti et al., 2012; Pawluski et al., 2020). Furthermore, the female sex has been shown to be a risk factor in the development of adverse drug reactions (ADRs) (Franconi et al., 2007; Moyer et al., 2019), which may be a result of hormonal differences between females and males, for whom drugs such as antidepressants were developed for and tested on.

Scientific research has relied on the male sex to establish physiological and pharmacological norms (Joel & McCarthy, 2017; Mielke Miller, 2021), and in that process has omitted the female sex. However, understanding the complexities of neurophysiology is necessary to form policies and guidelines that move towards a more precise and sex-inclusive medicine with regard to dosage, tolerability, side effects, and distinct treatment strategies that benefit the entire population (Biskup et al., 2020; Joel & McCarthy, 2017). Thus, there is an urgent need to understand the multiplicity of ways in which sex can alter the brain.

This paper argues that the further inclusion of females in neuropsychiatric and neuropharmacological research and trials in the coming years is necessary to accelerate and ameliorate the establishment of truly individualized medicine. To that effect, I examine previous and ongoing research and findings on how sex plays a critical role in neuroscience and will specifically examine MDD in that context.

Sex Bias in Neuroscience

The current knowledge available to clinicians about diagnosis, treatment, and prevention of disease originates from studies conducted on male cells, male mice, and males (Mauvais-Jarvis et al., 2020). Historically, the lack of female inclusion in clinical trials and research was justified by the need to protect the safety of females of reproductive age and their offspring (Fleisch et al., 2005; Mauvais-Jarvis et al., 2020). Furthermore, and perhaps more importantly, it was generally thought to be more challenging to study females due to fluctuating hormones throughout the menstrual cycle (Moyer et al., 2019). It was only in 1993 that the US National Institutes of Health (NIH) wrote the inclusion policy[1] into federal law that would ensure that it would be required to include females in biomedical research (Joel & McCarthy, 2017).

Nonetheless, sex bias and omission, referring to the lack of reporting or accounting for sex in studies, remains pervasive in pharmacology and neuroscience, along with several other scientific and biomedical fields (Joel & McCarthy, 2017; Mamlouk et al., 2020). In their review, Mamlouk et al. (2020) analysed primary neuroscientific research articles and found that along with 26% of articles only employing males, 44% of articles also employed females but did not consider sex as an experimental variable.

Although it can be argued that females are increasingly included in neuroscientific research (Fleisch et al., 2005; Mauvais-Jarvis et al., 2020), this inclusion does not provide scientific insight unless sex is taken into account as an experimental variable (Mamlouk et al., 2020). This is because the omission of sex as a variable has three unfortunate consequences. First, it overlooks the underrepresentation of females in research. Second, not

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[1]Women and Minorities as Subjects in Clinical Research

reporting the sex of participants may lead to a loss of scientific reproducibility. Finally, not addressing sex as a variable may lead to missed opportunities for discovering sex-specific neurological phenomena (Mamlouk et al., 2020).

Additionally, to date, sex differences are undeniable in most research areas and have been the focus of a growing body of research in neuroscience and neuropharmacology (Pawluski et al., 2020). Sex differences can be observed in neuroendocrine functions, stress response, cognitive processes, as well as neuropsychiatric diseases and their pharmacological treatments (Pawluski et al., 2020). These differences must be addressed, not only to ensure and improve female health, but also to deepen our current understanding of sex-specific effects in health and disease.

Intersection of Female Sex Hormones and Major Depressive Disorder

Sex significantly affects the risk for neuropsychiatric diseases, which can be exemplified by major depressive disorder (MDD) (Pawluski et al., 2020). Indeed, females are more than twice as likely to develop the disorder compared to males (Fernández-Guasti et al., 2012; Keers & Aitchison, 2010; Sommer, 2020). These differences can be accounted for by sex, or gonadal, hormones. It has been shown that progesterone and oestrogen have a profound and broad effect on neurochemistry and brain function, as they interact with early-life stress and genetic risk and thus contribute to risk of depression (Bale & Epperson, 2015; Pawluski et al., 2020).

Affective or Mood disorders are commonly associated with a dysregulation in the Hypothalamus-Pituitary-Adrenal (HPA)-axis, and it has been observed that sex differences in the incidence of MDD correlate with sex differences in HPA-axis function (Bale & Epperson, 2015; Fernández-Guasti et al., 2012). The HPA-axis is normally regulated by three hormones, namely corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol, and is activated following stress exposure (Zhu et al., 2021). However, in MDD patients, the negative feedback loop that ensures the regulation of cortisol release is dysfunctional (Fernández-Guasti et al., 2012). Namely,

it has been hypothesised that the female sex hormones, estrogen and progesterone, and their frequent fluctuations during the menstrual cycle may lead to a sensitized HPA-axis compared to what is observed in males (Dong et al., 2020; Fernández-Guasti et al., 2012). This would lead to a hyperactive HPA-axis and thus to overall higher levels of cortisol, which puts females at a higher risk of developing MDD (Dong et al., 2020; Zhu et al., 2021). Due to the frequently fluctuating female sex hormones, the clinical manifestations of MDD also differ in males of the same age, including emotional symptoms such as irritability, anxiety, and rumination (LeGates et al., 2019; Zhu et al., 2021). Interestingly, the incidence of new-onset MDD significantly decreases in menopausal females, whose estrogen production diminishes greatly through the loss of menstruation, to the extent that these females are susceptible to MDD to the same extent as males (Freeman et al., 2014; Herzog et al., 2019). This finding supports the crucial role that female sex hormones and their fluctuations play in the pathophysiological mechanisms of MDD (Herzog et al., 2019).

To summarise, MDD, which is considered to be a leading cause of disability worldwide (Dong et al., 2020), shows biological differences between the sexes in terms of sensitivity, presentation, and underlying mechanisms.

Adverse Drug Reactions and the Efficacy of Antidepressant Treatments in Females

Due to females being excluded from research and drug trials, most drugs have been prescribed to males and females at the same dose (Zucker & Prendergast, 2020). It has been increasingly observed that females are disproportionately affected by ADRs (Moyer et al., 2019; Yu et al., 2016). An ADR can be described as a harmful or unpleasant reaction resulting from the use of a medicinal product (Coleman & Pontefract, 2016). Data on ADRs are utilised by clinicians to prevent future hazards from occurring (Coleman & Pontefract, 2016). Females are 60% more at risk than males of exhibiting ADRs across all drugs, which could be the consequence of many biological and psychological factors relating to sex (Moyer et al., 2019; Zucker & Prendergast, 2020). For instance, one

could consider the fact that females have, on average, lower body weight, organ size, and brain volume, but have higher percentages of body fat, which affects both the distribution and absorption of drugs (Sommer, 2020; Zucker & Prendergast, 2020). Furthermore, responses to drugs are also influenced by the physiological changes that occur during the menstrual cycle, which involves hormonal fluxes across days, unlike male's hormonal variations that occur throughout the day (Islam et al., 2017). Thus, as medicine is moving towards individualised treatment strategies (Moyer et al., 2019), it is imperative that pharmacological studies consider the varying effects that neuropsychiatric treatments can have on all people.

In addition to the previously mentioned differences in risk and clinical presentation, males and females differ in their responses to antidepressant treatment for MDD (LeGates et al., 2019). Currently, commonly prescribed antidepressants for the treatment of MDD are selective serotonin reuptake inhibitors (SSRIs) and tricyclics (TCA), yet these are only effective for a fraction of the population and differ between the sexes (Bigos et al., 2009; LeGates et al., 2019). Therefore, delving into sex differences in the underlying neurobiology of depression could provide us with the potential to reveal novel targets for the development of antidepressants (LeGates et al., 2019). TCAs block reuptake of serotonin and norepinephrine, which is thought to contribute to their therapeutic action. However, at high levels, they can inhibit sodium channels and have been shown to increase the risk of suicide by overdose, particularly in females (LeGates et al., 2019). The latter has been found to occur due to a lower clearance of TCAs in females, which leads to higher plasma concentrations of the drug (Damoiseaux et al., 2014; Sramek et al., 2016). Studies have shown that females experience a worse therapeutic response to TCAs than males (Bigos et al., 2009; Duffy & Epperson, 2021; LeGates et al., 2019), which is accounted for by this higher plasma concentration that in turn leads to ADRs (Damoiseaux et al., 2014). Furthermore, it has been suggested that considering the modulatory effects of oestrogen, it can be hard for females to reach the narrow therapeutic window of TCAs (Keers & Aitchison, 2010).

Although there is evidence that SSRIs are a more promising treatment method for females suffering from MDD (Bigos et al., 2009; Duffy & Ep-

person, 2021; Herzog et al., 2019; Sramek et al., 2016), a study by Ekhart et al. (2018) relating to the use of SSRIs found that 68% of ADRs were reported by females, and most were found to be dose-related. Both TCAs and SSRIs, though effective on some level, have shown to be problematic for females, which can be linked to the varying pharmacokinetic profile females present with compared to men and includes differences in absorption, distribution, metabolism, and clearance (Damoiseaux et al., 2014).

Thus, despite neuropharmacological studies and research having proven that there are significant differences in the clinical presentation, underlying neurobiological causes, and mechanisms of MDD, as well as observations of ADRs, science still forces the same clinical practices on all. It may be more beneficial and pertinent to deviate from this notion and model MDD in males and females separately by focusing on the endophenotypes relevant to each sex.

Conclusion

It is clear that although there has been progress in terms of female inclusion in neuroscience and the sciences in general, there are still many disparities regarding psychiatric conditions, their treatments, and our understanding of them. Finding causal links, such as fluctuating hormone levels during the menstrual cycle or differences in drug metabolism, are essential for the understanding of sex-linked differences in the clinical presentation and treatment of disorders.

Sex bias and omission are heavily discussed topics in the literature deliberated in this paper, and it is necessary for future research to address these problems in order to take the fundamental step towards precision medicine that will benefit everyone. Such a step could, in time, be of use when prescribing drugs, and thus would prevent a large fraction of the population from experiencing dose-related ADRs.

Although hundreds of years of research conducted by, with, and on males cannot be replicated for females, we can utilize the current knowledge available about sex disparities in MDD to promote further research. Neuroscience is a rapidly growing field and researchers should ensure that any future research makes the conscious decision to produce

results relevant to the whole population. Advancing and deepening the currently available knowledge of the brain and its different interactions, depending on sex, would be a step forward for medicine to be more precise and individualized.

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