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Beating of hammers

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Abstract
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I've been investigating the connection between migraine and depression—two debilitating disorders with high comorbidity. My overarching goal is to unravel their pathophysiology and pinpoint associated risk factors to pave the way for more effective therapeutic interventions. The fruits of my labor is discussed in the introductory part of the thesis and comprises four first-author publications in international peer-reviewed journals.

In the first two projects, I worked mostly on the comorbid aspects of migraine and depression. I conducted a meta-analysis on the efficacy of onabotulinumtoxinA injections as a treatment for those grappling with both migraine and depression. The findings were promising, showing not only the treatment's safety and effectiveness but also hinting at a shared pathophysiology between the two conditions. The second project delved into the structural brain anatomy, utilizing voxel-based magnetic resonance imaging measures to explore subcortical volumes in migraine and depression patients. The distinct patterns observed suggest a nuanced relationship at the subcortical level.

Expanding beyond comorbidity, my research ventured into the occupational determinants of migraine, scrutinizing the impact of job-related factors on migraine prevalence. Leveraging data from the UK Biobank, the third project identified strong associations between migraine and specific job categories, setting the stage for future interventions and policies to enhance workers' well-being. Additionally, my exploration into the role of the cerebellum and brainstem in migraine pathophysiology, using the UK Biobank data, unveiled larger gray matter volumes in multiple cerebellar regions in individuals with migraines. This sheds light on potential mechanisms underlying migraine attacks, contributing significantly to our understanding and potential treatments for these challenging disorders.

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Dedicato a Pon

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I O. Affatato, T. C. Moulin, C. Pisanu, V. S. Babasieva, M. Russo, E. I. Aydinlar, P. Torelli, V. N. Chubarev, V. V. Tarasov, H. B. Schiöth and J. Mwinyi , “High efficacy of onabotulinumtoxinA treatment in patients with comorbid migraine and depression: a meta-analysis,” J Transl Med, vol. 19, no. 1, p. 133, Dec. 2021, doi: 10.1186/s12967-021-02801-w.

II O. Affatato, M. Miguet, H. B. Schiöth, and J. Mwinyi, “Major sex differences in migraine prevalence among occupational categories: a cross-sectional study using UK Biobank,” J Headache Pain, vol. 22, no. 1, p. 145, Dec. 2021, doi: 10.1186/s10194-021-01356-x.

III O. Affatato, A. D. Dahlén, G. Rukh, H. B. Schiöth, and J. Mwinyi, “Assessing volumetric brain differences in migraine and depression patients: a UK Biobank study,” BMC Neurol, vol. 23, no. 1, p. 284, Jul. 2023, doi: 10.1186/s12883-023-03336-x.

IV O. Affatato, G. Rukh, H. B. Schiöth, and J. Mwinyi, “Volumetric Differences in Cerebellum and Brainstem in Patients with Migraine: A UK Biobank Study,” Biomedicines, vol. 11, no. 9, p. 2528, Sep. 2023, doi: 10.3390/biomedicines11092528.

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Contents

1. Ouverture

> These fragments I have shored against my ruins
>
> ---
>
> *The Waste Land*
> *Thomas S. Eliot*

1.1 Brains in disorder

Let's start our journey with a story. It is a warm morning on the 14^{th} day of the spring month of Nisan. We are in Yershalaim, at the palace of Herod the Great. From the colonnade we see emerging the figure of the Roman procurator of Judea, Pontius Pilate. He is going towards the hall where he will be soon interrogating a man accused of inciting the crowd to destroy the sacred temple of Yershalaim. Pilate is sickened by the smell of rose oil which permeates the chambers of the palace. He reaches the hall where his secretary was waiting for him. He sits on his chair and the prisoner is brought in. Before the Roman procurator of Judea stands a man in chains with bruises all over his body. This man is Yeshua Ha-Nozri.

The interrogation starts. Pilate tries to stare at the man, but his eyes are clouded with suffering. He is in deep pain. For the whole interrogation, Pilate looks like a marble statue, trying to show all the severity and power of a soldier of Caesar, but completely still. He avoids any movement: even the slightest turn increases his suffering. He cannot think properly, he is unable to focus. Pilate his tortured by a deep pain, pulsating in his head. His condition is so terrible that he wishes for some poison to end it forever. While the symptoms are described along the chapter, the reader is informed already at the beginning on the nature of Pilate's suffering. It is the "invincible, terrible disease", something for which "there's no remedy [...], no escape" [1]. A crippling pain that affects half of the head: migraine.

This is not the only place in the book where we see a character suffering due to his or her health conditions. Mental illness features prominently in the story and it exerts great impact on the unfolding of the events. Bulgakov, a physician by education, uses the balance between health and disease throughout the book to draw a path towards the characters' inner sphere. What happens to their bodies, and especially their minds, is an important reflection of their moral struggles in an environment, in a city, that suppresses the individuals

rather than giving them space to grow.
At some later point in the book we find ourselves in Moscow, many centuries later. We are in a psychiatric clinic in some unspecified outskirts, by the river bank. It is late at night and one of the new patients gets a visit from another convalescent who managed to steal some keys from a nurse and then to make his way to the newcomer's cell. We learn that the intruder is called the Master, and not much more about his identity. He starts telling his story to the new patient, explaining how he ended up in a psychiatric clinic. We learn that the Master was previously working as a historian in a museum. Life was going well for him, but at one point he decided to quit his job to dedicate himself to the writing of a major literary work: a novel about the last days of Jesus Christ. The days passed by and he became completely immersed in the pursuit of his ambitious project. In this endeavor he was also supported by Margarita, the love of his life. After some time the novel was completed and the Master started reaching out for publishing companies. In his first attempt to publish his work he got a painful rejection from the editor. The Master was particularly hit by this event because the rejection was based on his political ideas and his social status rather than on the actual value of the novel. This event threw the Master in a state of deep sadness. Then a series of articles started appearing in the newspapers harshly criticizing the Master and his work. He became desperate and his mental health began deteriorating. Day after day he was drained by any sense of joy and purpose and he felt like drawing in the deepest darkness. He had nothing left to live for. The despair reached its highest as he attempted to end his life.

1.2 A tale of two illnesses

In the previous section I used a rather literary approach to introduce the two main characters of this thesis: migraine and depression. These two conditions have long been present in the history of medicine and looking at the evolution of their definitions through the ages is helpful to give a different perspective on how we understand and classify them nowadays.
The first unequivocal accounts of both disorders are found in the writings of the Hippocratic school. Migraine, *hemicrania* originally, was first described as unilateral throbbing pain sometimes preceded by visual symptoms, while depressive mood, defined as *melancholia*, has been described as long-lasting fear or sadness [2, 3]. The ancient philosophers explained the causes of these illnesses, as they would explain any other, with the theory of the four humors. This theory is attributed to the Greek philosopher Empedocles and claimed that our health state is controlled by the balance of four bodily fluids, or humors: blood, phlegm, yellow and black bile [2, 3]. Diseases, therefore, is caused by any imbalance between these fluids. It is important to highlight that, regarding

the diagnosis of melancholia, the ancient philosophers put high emphasis on the context. Sadness was considered a dysfunction only if the symptoms were a disproportionate response to a given cause.

The theory of four humors and all classical medicine went unchallenged for many centuries, through the whole antiquity, the Middle Ages and part of the modern times. Regarding migraine, two new major hypotheses on its etiology were developed between the 17^{th} and 18^{th} centuries, challenging the humoral basis of pathology. Thomas Willis proposed the first version of the *vascular hypothesis*, i.e. the idea that migraine is essentially a vascular problem. According to his view the cause of migraine attack was increased blood flow in cranial arteries that would in turn exert pressure on the trigeminal nerve [2]. Another important contribution came from Samuel Tissot who described in great details the symptoms of headache disorders. He also proposed the *neurogenic hypothesis*, i.e. the idea that the origin of migraine attacks was in the nerves that from the stomach reached the trigeminal system. The pain would then affect mostly the areas innervated by the trigeminal nerve [2]. Regarding depression, no major progresses were made until the 18^{th} century. Notably, the influential text *Anatomy of Melancholy* (1621), by Robert Burton, gave a powerful account of the classical tradition. Burton recognized three major components in depression: mood, cognition and physical symptoms. Moreover, Burton discussed the importance of individual variation in symptoms presentation and severity, as a consequence of variation in temperament [3].

Between the 19^{th} and 20^{th} centuries, there was an increasing improvement in experimental, clinical and statistical methodologies. The symptoms of migraine and depression were characterised in more details, reducing ambiguities from the past, and in general the treatment options for both disorders vastly improved [2, 3]. The definition of migraine and depression that are currently adopted are based on such scientific and technological advances. The diagnostic criteria for migraine were developed by the International Headache Society and, according to the latest classification, migraine is mainly divided in sub-categories based on the presence of aura symptoms (with or without aura) and on frequency (episodic or chronic) [4]. Migraine symptoms broadly comprise recurrent moderate-to-severe and long-lasting (between 4 and 72 hours) headache attacks. The headaches are usually unilateral, pulsating, aggravated by general physical activity and associated with nausea and/or phonophobia and photophobia [4]. Regarding depression there are two major and widely used frameworks where the symptomatology is defined: the International Classification of Diseases and the Diagnostic and Statistical Manual for psychiatric disorders. We will consider the former classification method as it is the one used in my studies. According to the 10^{th} edition of the International Classification of Diseases major depressive disorder is mainly characterised by depressed mood, loss of interest and enjoyment, reduced energy and libido, increased fatigue, disruption of eating and sleeping habits, sense of guilt and worthlessness, pessimistic and bleak views of life and future and suicidal attempt or plan. The symptoms vary in severity and should last at least two weeks to be considered a depressive episode.

1.3 What's in a name?

In the previous section, I briefly went through the different approaches used to understand and define migraine and depressive symptoms across the history of Western medicine. All the scientists that tried to address this issue had one fundamental question in their minds: what constitutes the disease? Apart from the obvious differences between the various approaches adopted to answer this question, we can see the emergence of several constant tendencies across history. On one side we have the detailed description of the symptoms, the signs of the lack of health as manifested in the individual patient. As we saw in the brief historical account, a great amount of effort has been devoted into give precise and appropriate description of the symptomatology. On the other side features prominently the problem of the etiology, the explanation of the causes that lead to sickness. The principle behind unraveling the etiology is that knowing the ultimate causes of the disease would lead to the definition of an appropriate treatment strategy and hopefully the remission of the symptoms and the restoration of the health status in the patient.
The relation between symptomatology and etiology introduces naturally a hierarchy of the levels of sophistication of the diagnosis. The most basic level is the symptomatic, i.e. the clinical presentation of the individual sign as manifested in the patient, followed by the syndromic level that accounts for the clustering of symptoms across populations [5, 6]. With the advancements of scientific inquiry, experimental techniques and methodologies, the clinico-pathological approach was developed, which aims at connecting the clinical manifestations to morbid anatomical and physiological changes [6]. This resulted in the theoretical improvement of the diagnosis sophistication to the level of the pathophysiology, that accounts for the biological mechanisms that lead to sickness, and of the etiology, i.e. the ultimate causes of the disease [5, 6]. The etiological level is the most important piece of information, the one that has the best explanatory power in defining a disease. Consequently, the etiology guides us to creating interventions that have the highest potential to cure the patient.
What are the implications for migraine and depression? In both cases there is currently no general agreement on their etiology and the diagnostic criteria are at the syndromic level [6, 7]. Moreover, as we saw in the previous section, the definitions of these disorders haven't changed significantly through history and this challenges the validity of the current diagnostic criteria. The major consequence of these problems is the difficulty in finding effective treatment solutions for most of the patients.

1.4 Rationale

Thus far I introduced the symptoms of migraine and depression, I gave a brief overview of their place in the history of medicine and I discussed their diagnostic criteria. But why migraine *and* depression? These disorders have remarkable distinctive features with negligible overlapping in the clinical presentation. Nevertheless, migraine and depression are related in several important aspects.

From a diagnostic perspective, their definition is based on a polythetic type of classification. This means that to get a diagnosis of migraine or depression an individual should manifest at least a few symptoms from a broad and heterogeneous variety of possible clinical signs. Moreover, as I previously showed, these diagnostic criteria are at syndromic level, they lack a strong etiological rationale, and experienced little modification for most of the history of medicine.

From an epidemiological perspective, migraine and depression are both highly prevalent and burdensome disorders [7, 8]. For migraine the age-standardised global prevalence is approximately 14.4% [9]. The prevalence of depressive symptoms is estimated to be as high as 30% [8]. Women are mostly affected, being twice more likely than men to experience migraine or depressive symptoms [7, 8]. Moreover, they have a high degree of comorbidity: having one of the two disorders significantly increases the risk of developing the other one. These associations were studied mostly in cross-sectional settings, but evidence on the causal link between migraine and depression is available also from retrospective and prospective cohort studies [10].

These common features constitutes the rationale behind the research discussed in this thesis. The material is presented in two sections. In the first part of the thesis I will discuss the principles and ideas behind the research that I conducted and the choices I made. In the second part I will present the results in the form of published papers. In the latter section the reader can find the complete account of the technical details.

2. Aims

In this way I shall follow you, and
wherever you place the extreme edges, I
ask: what happens to the arrow at last?

De rerum natura
Titus Lucretius Caro

The overall goal of the papers included in this thesis was to study the pathophysiology of migraine and depression. To achieve this goal we used several approaches, from brain morphology to pharmacology and epidemiology. While all the papers are characterized by the same underlying purpose, each of them had specific research questions and aims, summarised as follows:

- Paper I: how effective is onabotulinumtoxinA as a treatment for migraine with comorbid depression? We addressed this research question in a meta-analytical setting to assess the efficacy of this pharmacological treatment in improving migraine and depressive symptoms as well as to shed some light on the possible common pathophysiology of these two highly comorbid conditions;
- Paper II: what are the job-related factors more strongly associated with migraine? Job is a fundamental part of our lives and identifying the occupational factors that might hinder the workers' health is of paramount importance because it enhances a better understanding of the pathology and it informs policy-making to improve the work environment;
- Paper III: is the putative common pathological pathway of migraine and depression reflected in brain morphology? In this study we investigated anatomical differences at the level of several sub-cortical brain regions to assess whether some areas were similarly affected in patients with migraine as compared with individuals with depression;
- Paper IV: is the pathophysiology of migraine reflected in volumetric differences in the cerebellum and the brainstem? Recent studies have posited an active role of the cerebellum and the brainstem in migraine pathophysiology. In this study we further investigated this hypothesis.

3. Materials

> Of what materials was I made that I could thus resist so many shocks, which, like the turning of the wheel, continually renewed the torture?
>
> *Frankenstein*
> *Mary Shelley*

3.1 Literature databases

The first project was a meta-analysis of the published literature [11]. The literature search was based on the datasets PubMed, Web of Science, and Scopus. We considered all the papers written in English that were published before October 30^{th} 2020. The literature search was done independently by Oreste Affatato and Victoria S. Babasieva and any discrepancy or disagreement was discussed under the supervision of Jessica Mwinyi.

3.2 The UK Biobank cohort

The other projects were all based on data from the UK Biobank study [12, 13, 14]. The UK Biobank is a large population-based study aiming to provide data for a comprehensive investigation of health and disease [15]. It is a large-scale biomedical resource that contains a broad variety of data from over half a million UK individuals. People registered with the National Health Service, aged between 40-69 years, and living within a range of 25 miles from one of the 22 Assessment Centers (located in England, Scotland, and Wales) were invited to participate [15]. During the recruitment process, a total of 9.2 million invitations were sent, and 503 325 participants were eventually recruited (corresponding to a 5.47% response rate).
The participants were assessed at baseline between 2006 and 2010. The volunteers answered touch-screen questionnaires and computer-assisted interviews, aiming to collect information on sociodemographic factors (such as ethnicity, income, employment status, and education), family history, early life exposures, environmental, psychosocial and lifestyle factors (such as shift work, smoking habits, alcohol consumption, diet, mental health, and social support).

Physical and functional assessments were made, such as blood pressure, heart rate, and anthropometric measurements. Blood, saliva, and urine samples were also collected. Multimodal imaging data were collected between 2016 and 2019 [15, 16]. Overall, this database comprises a wide range of in-depth data, from genetics and proteomics to health status, cognition, lifestyle, and brain imaging.

3.2.1 Ethical approval

Ethical approval for the UK Biobank study was granted by the North-West Multicenter Research Ethics Committee (permission UKB 57519). The Regional Ethics Committee of Uppsala (Sweden) approved the use of UK Biobank data for the studies included in this thesis (2017/198).

3.3 Funding

This PhD research was funded by WOMHER, Uppsala University's Center for Women's Mental Health.

4. Methods

> The Dao that can be trodden is not the eternal Dao. [...] The Dao is like the emptiness of a vessel.
>
> *Daodejing*
> *Laozi*

4.1 Literature search and meta-analysis

The meta-analysis project was done in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17], later updated in a more recent statement [18]. The PRISMA statement is the result of a collaboration of experts in meta-research and other stakeholders, initiated in the mid-'90s, that aims at providing tools to carry out high-level meta-analysis, ensuring quality, transparency, and reproducibility [17, 18]. In compliance with these guidelines, I reported the protocol of the literature search, the selection process, a qualitative assessment of the studies included as well as the rationale and the results of the statistical analyses.

Given the small number of studies investigating the efficacy of onabotulinumtoxinA as a treatment for migraine comorbid with depression and given the selection criteria, I was able to include only a few studies in the analyses. Therefore the results ought to be considered with caution: they represent a first step in summarizing the evidence of the efficacy of this therapy administered in patients with comorbidity.

4.1.1 Empirical Bayes method

One of the main goals of a meta-analysis is to produce a robust summary estimation of the effect of the individual studies under consideration [19]. In our case, while all the studies followed the same protocol for the administration of onabotulinumtoxinA, they differ regarding important aspects such as underlying study population, selection criteria, demographics distributions (e.g. age, sex), and assessment of outcomes and baseline characteristics. The observed effect is expected to vary across studies due to these structural differences and not only because of pure sampling variation. To account for the effect of the variation across studies I used a random-effects approach [19]. Let Y_i be the observed effect size of the i^{th} study, θ the true underlying effect, ζ_i the variation across studies, and ε_i the sampling error. A random-effects model could be expressed as

$$Y_i = \theta + \zeta_i + \varepsilon_i, \quad \zeta_i \sim \mathcal{N}(0, \tau^2), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma_i^2)$$

Where τ^2 is the variance across studies and σ_i^2 is the within-study variance. To estimate the true effect θ we need to estimate τ^2 first. I used the empirical Bayes method to estimate the across-study variance mainly because of the small number of studies that I could include in our analyses [20, 21]. Bayesian inference performs better than frequentist methods in small sample size settings. This follows from the fact that classical methods are justified by their behavior at large sample sizes, while Bayesian methods don't have this limitation [22].

4.1.2 Qualitative assessment of the literature and potential bias

Another important part of the meta-analysis is the qualitative assessment of the literature to complement the statistical analyses. I reported for each study the eligibility criteria, the demographic statistics of the sample (e.g. sex and ethnicity), the criteria and scales used to assess migraine and depressive symptoms, and the overall duration of the study. Moreover, I discussed side effects, adverse events, and discontinuation from the trial.
The assessment of the risk of bias plays also a central role in a meta-analysis. Amongst the many possible sources of distortion, publication bias is one of the most ubiquitous and impactful, especially in meta-analyses [23]. Even though I partially addressed the risk of bias from the individual studies in the qualitative assessment of the literature, I didn't proceed with a formal publication bias analysis because of the small sample size [19, 23].

4.2 Structural MRI

Anatomy is the first step in medicine towards the understanding of pathology. This is true also for neuro and psychopathology [24]. While in the past the study of neuroanatomy was strictly *post mortem*, nowadays it can be studied *in vivo* [24]. Amongst the many neuroimaging techniques, structural magnetic resonance imaging (MRI) is one of the most prominent and widely used. Structural MRI can be used to construct a detailed map of the brain's gross anatomy, given it's power to differentiate between brain regions [25]. While in the clinical practice it is mostly used for identifying lesions, injuries or deformations, in research settings structural MRI remains a valuable technique to study the

associations between alterations in the gross anatomy of brain structures and pathology [24, 25].
Two of my projects are part of a series of studies employing structural MRI techniques to shed light on migraine and depression pathophysiology from the perspective of the gross anatomy variation in certain brain regions [13, 14]. Even though the actual pathological mechanism of migraine and depression might not be reflected clearly at the level on the gross anatomy, this kind of study provides important evidence to improve our understanding of such conditions.

4.3 Inferential methods and causal models

The other three papers included in this thesis are observational studies, thus differing substantially from the first one which was a meta-analysis of clinical interventions. The observational nature of such studies brings further challenges from an inferential point of view that need to be addressed.
As I stated at the beginning, my scientific questions are inherently causal and to address causality when no experiment is done is an hard task. Statistics alone is not able to help us and further assumptions are to be made to get an approximate causal interpretation of my statistical models. In this section I will discuss briefly the challenges that I encountered from a causal modelling perspective and the strategies that I adopted to address them.

4.3.1 Causal models

Amongst the many frameworks of causal inference there are four major types employed in medicine: graphical, potential outcome, sufficient component and structural equation models [26]. These approaches capture different aspects of causal inference, but they are all related to some extent and can be used to complement each other [27]. The main approach I used was the graphical model, whose most prominent tool is the directed acyclic graphs (DAGs), like the one in Figure 4.1.

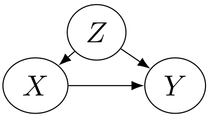

Figure 4.1. An example of a Directed Acyclic Graph.

A graph is made by *nodes*, representing variables of interest, and by *edges*, which are lines connecting them. A graph is said to be *directed* if the edges are arrows and it is *acyclic* if the arrows do not form any close loop. A given DAG is said to be *causal* if the arrows represent a causal model of the world,

i.e. they represent causal relationship between the variables [26, 28].
Causal DAGs are a powerful tool to display our causal assumptions on a certain phenomenon. They allow to see whether to expect a statistical association, assuming the model to be the correct one. They also allow to eliminate spurious or uninteresting associations, which constitute the most important problem in observational studies.
As previously mentioned, my research questions on pathophysiology of migraine and depression are inherently causal questions and can therefore be stated as causal models using cDAGs. In an observational setting, the effect of the exposure of interest would in general mixed up with the effect of other factors. This mixing up is mostly due to *confounding*, i.e. the presence of a common cause of the variables of interest, or selection bias. To address this problem and disentangle the effect of interest from the effect of other factors one can use cDAGs. It can be proven mathematically that once a cDAG is established one can use it to condition the statistical model to eliminate the effect of confounding factors [26, 28].

4.3.2 Regression

The cDAG approach is a powerful tool, but it remains a qualitative assessment of causal relationships and it needs to get coupled with a quantitative method to produce an estimation of a causal effect. We adopted the regression model, one of the most widely spread methods in causal inference [22, 28, 29, 30]. Referring back to Figure 4.1, a linear regression model can be stated as

$$Y = \alpha + \beta X + \gamma Z + \varepsilon$$

where Y is the outcome, X is the exposure of interest and Z is another variable that can influence directly or indirectly both outcome and exposure. With ε I indicate the random error, by α I indicate the intercept and β, γ are the coefficients of the variables. The regression coefficients can be used to estimate the association of the variable of interest X on the outcome Y, other variables being equal. Conditioning within the levels of the other variables removes the effect due to differences in other factors and isolates the effects that one wants to measure, getting the estimate close to the *ceteris paribus* (i.e. other things being equal) condition which is the basis of causal inference [30].
Even though my research questions have been framed in a causal inference framework, it would be risky to interpret my estimations from the regression models as actual causal estimations. The main problem derives from the fact that the cDAGs that I proposed are not complete. This is both due to the unmeasured variable problem and for the existence of unknown causal mechanisms. Moreover, the lack of a timeline doesn't allow to establish if the exposure caused the outcome or vice versa. These and other issues prevent us for giving a fully causal interpretation to the estimations [22, 26, 29].

4.4 Further methodological considerations

In this section I briefly discuss a few issues that might raise concerns about the analytical strategies that I adopted. In particular, the two major issues that I would like to consider are the multiplicity problem and the hypothesis testing statistical framework. Both these issues have fostered long-lasting debates across the scientific community and I don't have the ambition to propose any resolution in this setting. Here I would rather clarify and justify my positions to help the reader to interpret the results I produced in my work.

4.4.1 The multiplicity problem

One of the most common concerns in applied statistics is the *multiplicity* or *multiple comparisons* problem. In classical null hypothesis testing, when we perform an inference we are mostly concerned about the false positive error. When many tests are done simultaneously, the false positive rate increases just because a large number of inferences have been produced. There are many ways to address this issue, and they mostly involve setting a stricter threshold for statistical significance or inflating the interval estimators [31]. While the multiplicity problem is a real phenomenon, many of the approaches commonly adopted to address it have been criticized [31, 32, 33]. Leaving aside the important issue of the across-studies correction, one of the arguments is that having a stricter threshold for false positive findings would inflate the false negative findings. The false positive/negative discovery rate are highly contingent on the context, they depend on the a priori plausibility of the existence of an effect. When we are already confident that an effect is to be expected the increase of the false negative findings is an issue [31, 33]. Moreover, one should also consider the influence of the researcher's degrees of freedom. The researcher has countless ways to analyze the very same dataset to address the same research question and this further worsens the multiplicity problem [22, 34].
There is no universal solution to this problem. The strategy that I adopted in my work consisted in proposing the most comprehensive statistical model, to the best of our understanding of the research question, and to highlight the fact that I didn't correct for the multiplicity problem. I choose not to correct because my research is mostly a confirmatory project of previous studies, and therefore an effect is expected to some extent. In any case, the reader should always consider that I didn't make any multiplicity correction when producing my results.

4.4.2 Hypothesis testing

The scientific questions that I addressed in all the four projects have in common a key feature: they are all estimation of effects. Even though the simple models I adopted do not allow for a proper causal interpretation, one can more safely interpret my findings as estimations of associations or comparisons between two or more groups. The natural quantitative approach to answer this kind of questions is estimation statistics, and that is the approach I adopted within the frequentist framework. For this reason I didn't consider using the null hypothesis testing approach. Many authors, however, opt for complementing this strategy with null hypothesis testing. In these cases, the null hypothesis is assumed to be the no effect, $\beta = 0$, a significance threshold is set and a p-value is calculated. If the p-value is below the threshold the effect is deemed significant, otherwise non significant.

We decided not to focus on any test of null hypothesis because this whole approach suffers from serious limitations. First, the null hypothesis testing framework enforces a dichotomy, between significant and non significant findings, that in most cases has no scientific rationale [26, 35, 36, 37, 38, 39]. Second, the p-value is a concept often misunderstood and focusing on the null draws away the attention from the other values which are compatible with the data and the statistical models [36, 40, 41, 42, 43, 44]. Third, researchers usually consider only one null hypothesis, the effect being a mathematical zero, and they test only that. However, there is usually a range of values around zero that correspond to a scientific null value. Focusing on only one value as the null is inappropriate as many other values which correspond to a biological zero effect may also be compatible with the data and the models.

What it is known nowadays as the null hypothesis testing approach stems from two schools of thought that originated a hundred years ago: the null hypothesis and significance level proposed by Ronald A. Fisher and the decision-making approach based on two competing hypotheses proposed by Egon Pearson and Jerzy Neyman. These methods were developed to answer specific technological and scientific questions that were common at the time. Science has changed since then and we should move towards adapting to new methods to address the specific challenges of our time.

4.5 Open Science

Open Science is a composite framework that aims at making scientific materials in their various forms (e.g. data, results, educational resources...) as accessible as possible to everyone in the society. Open Science, in its different aspects, is generally supported and encouraged by the European Union and by the Swedish government. In compliance with these general guidelines all the research projects included in my dissertation have been published in Open Access format. Moreover, due to my commitment to transparency and Open Science in general, in the second part of my PhD studies I started working with the open-source R software and publishing the scripts of all the data analyses included in my research projects. They are openly accessible in my GitHub page: `https://github.com/OresteAffatato`.

Finally, I am also strongly committed to teaching and to openly accessible educational resources. Therefore, I made freely available in my GitHub page also most of the teaching material that I created for my Master students during these years.

5. Results and Discussion

He knew nothing except just the fact of his ignorance.

Lives of Eminent Philosophers
Diogenes Laertius

In this chapter I will discuss the results of the research projects which are the subject of this thesis. The chapter is divided into three main parts, according to the approach taken to answer the corresponding research question: the pharmacological, the epidemiological and the morphological perspective.

5.1 Healing toxins

Treatment with onabotulinumtoxinA is one of the recent innovation in therapeutic strategies for migraine and depression. While previous meta-analyses estimated the efficacy of this treatment for the monomorbid condition, either migraine or depression, my work is the first pooling the evidence from clinical studies addressing the comorbid condition [45, 46].
In my study (Paper I) I found that the treatment with onabotulinumtoxinA leads to overall improvement in depressive symptoms as measured by several self-report inventories. The questionnaires are tools designed to assess the severity of depressive symptoms across three main dimensions, emotion (feeling down, hopeless, tired), cognition (sense of guilt, difficult in concentrating) and behavior (sleeplessness, appetite). Since they provide an overall score, it is difficult to see from the data I used in which specific domain the intervention has improved the condition of the patient. Even under this limitation, these inventories remain a useful tool to assess overall improvement. The onabotulinumtoxinA treatment leads also to a decrease in migraine frequency, severity and impact on normal daily activities, thus promoting a general betterment in the quality of life of the patients.
How does this therapy lead to such reduction in symptoms' burden? There is no universal consensus on the underlying reason for its efficacy, but there are several lines of evidence that can explain its therapeutic effects. *In vitro* experiments have shown that onabotulinumtoxinA inhibits the release of neurotransmitters and neuropeptides known to play an integral role in migraine pathophysiology, such as the calcitonin gene-related peptide and the substance

P [47]. It also reduces the expression of pain-sensing receptors on the plasma membrane and modulates immune cell activation as well as neuroimmune balance in cytokine secretion [47].
Regarding the influence on depressive symptoms several possible explanations have been proposed. OnabotulinumtoxinA can exert an influence on mood regulation by inhibiting the release of substance P [47]. The cosmetic benefits might also play a role in creating a positive feedback loop [48]. Another possible explanation it is the inhibition of the emotional feedback of facial expressions to the brain. The complex of corrugator muscles is one of the most prominent center for displaying negative emotions and thus the paralysis of this area due to the effect of onabotulinumtoxinA injections would hinder the negative emotion feedback to reach the brain [48]. It is also possible that the improvement in depression might be mediated by the improvement in migraine symptoms: the decrease in headache frequency and severity can exert a great positive influence in the patients' lives and therefore lead to an overall improvement on quality of life and mood.
While my work done in Paper I can be regarded as a first step in assessing the efficacy of onabotulinumtoxinA treatment for the migraine with comorbid depression phenotype, it is affected by several limitations. First, it is a small-scale meta-analysis, comprising ten studies. When more clinical research will be published it would be safer to draw stronger conclusion on a meta-analytical level. Another major limitation is due to the publication bias. Meta-analysis tend to give overconfident and overoptimistic estimates due to the fact that they are based solely (or mostly) on published research, which consists mostly of positive and relatively large (i.e. at least two standard errors away from the null to hit the statistical significance threshold) findings. This is an issue irrespective also of the bias due to conflict of interest.

5.2 Work in progress

Paper II aimed at investigating the associations between a broad variety of job-related features and migraine diagnosis. In particular, in this work I wanted to study the differential impact of potential work-related stressors in men and women separately, so that my work could help to establish more tailored interventions. Job and its influence on peoples' health is a complex topic that ought to be investigated in a multidisciplinary way. Moreover, given the complexity of interaction of many variables it can be difficult to identify and estimate a precise causal effect on which plan a future policy change to improve the health of the workers. Lastly, as for any study, the soundness of the results should be weighted against the quality of the data available and their reliability in measuring the underlying construct of interest, as well as the causal and statistical models used to analyse them.
In my analysis of the association of different types of jobs, as coded by the Stan-

dard Occupation Classification 2000, with migraine diagnosis I found slightly different pattern depending on sex. Highly qualified and managerial jobs, such as associate professional and managers, are protective against migraine in men, as compared to elementary occupations. In women I observed a tendency of overall no large differential prevalence (or odds) in the various job categories as compared to the elementary occupations reference. Even considering that the estimates are characterised by different levels of precision, the reasons for these difference might be several. For example, for women the risk to develop migraine might be independent of work-related stressors. On the other side, the reason behind the possible protective effect of high qualified occupations in men could be due to better access to healthcare providers, higher income and financial stability and their implications. Another reason of this differential pattern might be originated by chance due to high variability in sample size in each job category.

Job-related physical strain might also exert negative impact on workers' health. We found that migraine resulted to be more prevalent in men involved in highly physically demanding jobs. The reason why this happens is yet to be established as there is conflicting evidence in the field [49]. Moreover, most of the interest in the impact of physical activity on migraine has been studied in the context of leisure-type physical activities, such as sports, and not in the context of job-related physical strain exposures [49].

Lastly, I found that in women, migraine appears to be more prevalent in jobs involving shift work. Also in this case the evidence is conflicting [50]. The most plausible reason why shift working, especially night shifts, might increase the risk of migraine attacks is the disruption of the circadian rhythm [50].

This study is affected by several important limitations. First, while the UK Biobank cohort comprises more than half a million participants, only a fraction of them answered all the work-related questionnaires, thus decreasing importantly the effective sample size for the statistical analyses. Another important limitation is due to the fact that I couldn't assess if the migraine diagnosis happened before or after starting the job indicated by the participant in the occupation questionnaire. One important consequence of this is the difficulty in establishing the causal direction of the associations. Moreover, the UK Biobank cohort comprises mostly older people, while the peak of the prevalence in migraine is between 35 and 39 years [7].

5.3 The shape of matter

Structural magnetic resonance imaging is a powerful tool to study association between morphological changes in the brain and any other clinical or biological phenotype. The grounds for studying these associations are found on the possible reflection of pathophysiology at the level of the gross anatomy. Paper III and IV are part of a large tradition of structural MRI studies that aimed at

investigating the relationship of differences in brain volumes between people with migraine or depression and healthy controls. The novelty that I aimed to bring in the field lies mostly on the statistical modelling strategies that I propose and the larger sample size.
Regarding migraine I found larger gray matter volumes in several cerebellar sub-regions, namely V, VIIIa, X and crus I, than controls. Moreover, I estimated positive medium-to-high correlation between all the cerebellar subregions implying that the change in size in the region predicts a linear increase in the others as well. Even though the estimates were characterised by high variability in precision, it is likely that the cerebellum is overall larger in people with migraine than controls. Recent evidence showed the involvement of the cerebellum in pain modulation. This supports the possibility of its involvement in migraine pathophysiology, together with the fact that it is innervated by the trigeminovascular system [51].
At the sub-cortical level I found larger caudate nucleus and thalamus in migraineurs than controls. The caudate nucleus is part of the dorsal striatum, a fundamental element of the motor and reward systems, while the thalamus is part of the diencephalon and is also involved in the motor system as well as in regulation of sensory signaling, consciousness and sleep [52]. Both the caudate nucleus and the thalamus have been shown to play a major role in nociception, pain modulation and migraine pathophysiology [7, 51, 53, 54, 55]. Given my results, what I hypothesize is that abnormal brain activity at the level of the caudate nucleus and the thalamus might be reflected in the morphology of these regions.
I also found larger volumes in the amygdala and the putamen in people with depression than controls. The amygdala is part of the limbic system, located in the temporal lobes, and it is known to play a major role in memory and emotional responses (such as anxiety, aggression and fear), while the putamen is located at the base of the forebrain and it is part of the dorsal striatum, together with the caudate nucleus, and it regulate the motion at various stages [52]. The involvement of the amygdala in depressive symptoms pathophysiology is supported by several lines of evidence [56, 57, 58]. The role of the putamen in depression has not been fully elucidated, but there is evidence of its involvement especially through the reward and learning circuitry [59, 60]. Also in this case, the difference in gross anatomy in this region might represent a reflection of dysfunctional activity at molecular level.
As mentioned above, a positive aspect of these studies on the association between migraine or depression diagnosis and volumetric differences in several brain regions lies on the statistical methods. Using this dataset I was able to go beyond the simplistic hypothesis testing framework and were able to take into account several potential sources of bias. Moreover, another important difference compared to previous studies lies on the larger sample size. However, there are some other issues to be considered. A major limitation of my work is the cross-sectional design of the studies. Even though the scientific questions

were posed in a strictly causal framework it is not possible to draw a causal arrow from exposure to outcome. Moreover, the sample comprises mostly older people and this hinders the generalizability of my results, especially in the case of migraine.

6. Coda

I know not what tomorrow will bring

Last words
Fernando Pessoa

6.1 Theme and Variation

The works that I presented add some pieces to the complex puzzle of the pathophysiology of migraine and depression. In doing this research I put always emphasis on considering both the environmental and social determinants of the disease together with its biological aspects.
Regarding migraine there are multiple environmental risk factors, from stressful life events to physical activity, social support and education [61]. In line with this area of research, one of my projects explored one of the most important social aspects of our lives: the work environment. I considered a broad variety of occupational categories and job-related features and my results can be used as a pilot study for more specific investigations and interventions. Another important feature of my work is the segregation of the analyses by sex. This constitutes contribution in designing future policies that can improve the work environment in a more effective and equal way.
The other works aimed at unraveling the pathophysiology of migraine and depression at molecular and anatomical level. The most plausible mechanism leading to migraine and depression onset is mediated by neuroinflammation. From a pharmacological perspective I showed that inhibition at peripheral level of neuronal activity leads to a reduced release of several neurotransmitters known to mediate migraine and depressive symptoms. From an anatomical perspective I provided evidence that abnormal activity in certain sub-cortical areas and the cerebellum, where biomarkers such as calcitonin gene-related peptide and substance P are expressed, is associated with migraine and depression diagnosis.
Despite the general advancements in understanding complex diseases like migraine and depression, there are several challenges that needs to be addressed. A widely accepted theory that explains the etiology of these diseases is still not available and this has crucial consequences. As I discussed in the introduction, the diagnostic criteria, lacking a consensus on the etiology, are still at the syndromic level. This limits the efficacy of the treatment strategies and

the power of the prognosis. Moreover, the diagnosis is polythetic, namely two individuals might be diagnosed with migraine (or depression), but having little or no overlap in their symptoms. Giving the same label to different phenotypes with negligible common features implies identifying with the same category two different underlying constructs. This has important consequences in clinical and pre-clinical research and practice. For instance, the polythetic nature of migraine and depression diagnosis is at the basis of the large variation and heterogeneity found in my studies as for the rest of the neuropsychiatric literature. This in turn affects negatively the development of therapeutic strategies both in the form of pharmacological treatments and psychological interventions. This issue is also reflected in the high variation in response rates, side effects and partial response of specific medications commonly administered to treat migraine and depression [3, 8, 62].

6.2 Crescendo

In the previous section, I highlighted the current problem with the diagnostic criteria. How could it be addressed? A candidate theory that aims at explaining the etiology of a disorder should incorporate all the solid evidence that was produced so far under the framework of the other theories. Moreover, it should include both environmental, social, biological and genetic factors and harmonize them in a unifying etiological framework. One good candidate theory for migraine and depression is offered by evolutionary medicine, namely the application of the theory of evolution to human health and disease.

Evolutionary medicine addresses the issue of the disease as deviation from the normal functioning of our organism. Our body has been shaped over millennia by several evolutionary forces, such as natural selection and mutations. The result was to increase our chances of reproductive success in response to the challenges of the environment in which we lived [63]. In this framework disease is not something which has been the result of natural selection. It is difficult to believe a clinical presentation that we consider disorder have been selected because they increased our fitness, i.e. our reproductive success. Instead, disease is conceptualized as a consequence of our vulnerability due to evolutionary-determined traits interacting with some biological and environmental circumstances [63, 64].

Evolutionary medicine expands and complements the current approach to the understanding of disease of the mainstream medicine approach. The established way of addressing the definition of a disease is by asking questions on the proximate causes, namely how the individual developed the condition and the how underlying trait works. The former question relates to the developmental changes in the individual, while the latter relates to the normal function of the mechanism under consideration. These two questions, on how the individual trait works, have been developed in 1951 by the biologist Er-

snt Mayr and were later complemented with two evolutionary questions by the ethologist Nikolaas Tinbergen in 1963 [65]. Tinbergen argued that to have a complete picture of the function of a trait we should investigate its evolutionary history and its adaptive significance. Collectively, the two proximate questions together with the two evolutionary ones are known as the Tinbergen's four questions and constitute an important framework to have a more complete understanding of human disease, addressing the definition of normal functioning of a trait considering both the proximate and evolutionary mechanisms [65, 66, 67].
Another important feature of evolutionary medicine is that it naturally combines genetic and biological components of a trait with the environment. Mismatch is an example of such an interplay. Mismatch happens when a trait of an organism cannot adapt quick enough to a new environment. It can be due to spatial changes of the environment, for example due to migration, or temporal changes, for example due to cultural innovation.
Regarding depression, scholars working within the evolutionary framework proposed several plausible explanations. Sadness is mainly conceptualized as a reaction to cost-benefit evaluations in situations of threats. Social competitions are an example of such situation and a sadness response induces a resource-saving strategy when facing an uncertain threat. Depression is therefore considered an abnormal sadness response to such stimuli [66]. Similarly, migraine has been associated to the evolutionary function of pain, the main symptom of headache disorders. Sensation of pain is commonly considered a normal physiological response to environmental threats, triggering prompt avoidance behaviors [63]. Consequently, it has been postulated that migraine is a maladaptive activation of the otherwise normal adaptive responses [68, 69].

6.3 Finale

In May 2023 I had the opportunity to participate to the FENS annual conference in Portugal with some friends. On that occasion, professor Elena Cattaneo was invited to deliver the last plenary lecture. She went on stage and started presenting her work on the Huntington's chorea. After presenting her results of years and years of experiments, she started talking about why she decided to study such a disorder. It was because of a meeting, an event. She met a researcher when she was working at MIT, in Boston, that was deeply committed into finding a cure for the Huntington's chorea. Some members of her family suffered from it and she decided to dedicate her life not only to find a treatment, but also to give more visibility to this disease and more voice to the patients. Cattaneo, as the story goes on, was deeply moved by her story and she decided herself to work on this task, with the same attitude: having the person, the individual, at the center. Apart for her strenuous research efforts,

Cattaneo together with others from the association HDdennomore (HD hidden no more) organized an international meeting on May 2017 in the Vatican City. Huntington's chorea families gathered there for the event from all across the world, especially from South America. The Pope publicly recognised the disease and helped focusing the spotlights on this condition. To give to these people visibility, recognition and hope. To make it hidden no more.
Cattaneo gave a real masterclass on what it ultimately entails to be a scientist in the medical field. Even though the research is mostly frustrating, difficult, uncertain and the career is the most unstable, we shall never forget why we are doing this. What is the purpose, the endgame. And that is the message I took back with me. I cannot predict what is going to happen, what I am going to do in the future. What I can say is that I will try my best to have the patient in my mind, following and inspired by Cattaneo's example.
To end where we started, this is the sense to all of this work. To help those in need and to try our best to help them here and now. To strive for a different and better way of doing research that could give a different ending to the story of the Master and Margarita.

"We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.
Through the unknown, remembered gate
When the last of earth left to discover
Is that which was the beginning;
At the source of the longest river
The voice of the hidden waterfall
And the children in the apple-tree
Not known, because not looked for
But heard, half-heard, in the stillness
Between two waves of the sea."

- Little Gidding, Four Quartets, Thomas S. Eliot

7. Ackdnowledgments

No poet, no artist of any art, has his complete meaning alone.

Tradition and the Individual Talent
Thomas S. Eliot

I am a very lucky piece of shit. And if I managed to travel a long distance it's mostly because of the support of the loving people that I have around me. My deepest gratitude goes to all of you.
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তারপর স্পষ্টতই আসে সালাহউদ্দিন। তোমার শুরুতে অফিসের সঙ্গী ছিলাম এবং আমার প্রথম বন্ধুত্বের মধ্যে একটি। আপনার ফুসফুসে প্রচুর সিগারেট, আপনার লিভারে প্রচুর অ্যালকোহল, তবে সর্বোপরি আপনার হৃদয়ে অনেক স্বপ্ন। আপনি আমাকে স্বপ্ন দেখার গুরুত্ব মনে করিয়ে দিয়েছেন। আমি সর্বদা আপনার শক্তি এবং ইতিবাচকতা আমার সাথে বহন করব।

ترقی پر طور کے شخص محقق ایک مجھے نے آپ ملکہ۔ کی دفتر ہمارے یقیناً۔ گل، ملکہ پھر مخلصانہ اور زیادہ بہت میری سے دعاؤں اور حکمت اپنی نےہمیشہ آپ اور ہے دیکھا کرتے ضرورت اور صلاحیت کی کرنے اندازہ صحیح کا لوگوں اور حالات آپکی میں ہے. کی مدد ہوں۔ کرتا قدر سے دل کی خلوص اور محبت آپکی میں کرنے مدد کی مندوں

Puisque nous parlons de notre bureau, du règne de la reine Gull, nous devons parler de Gentreau. Meuf, tu es la meilleure! Tu es la preuve qu'il y a du bon en France. Nous nous sommes tellement amusés ensemble. Tu es extrêmement intelligente et un excellent exemple pour moi, en tant que chercheur et en tant que personne. Tu m'as beaucoup appris. Mais tu es avant tout une belle personne et une grande amie. Le souvenir de nos rires ensemble me réchauffe le cœur.

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फिर दिव्या है, मेरी छोटी दिव्या। आप एक खूबसूरत इंसान हैं और मैं आपके लिए और आपके द्वारा हासिल किए गए लक्ष्यों के लिए हमेशा खुश हूं। दूर होते हुए भी, शुक्राणु के प्रति हमारा जुनून हमें जोड़ें रखता है। मैं हमेशा आपकी खूबसूरत मुस्कान अपने साथ रखता हूं। फिर मुझे अपनी भारतीय जुड़वां मेघा को धन्यवाद देना है। आप स्टेरॉयड और टिक्का मसाला पर मेरा संस्करण हैं। आप भी असाधारण व्यक्ति हैं, सामान्य से हटकर। मैं आप के साथ बिताए सभी पलों और खासकर हंसी-मजाक के लिए आभारी हूं। जब आप हस्ती हैं तो दुनिया एक बेहतर जगह लगती है। फिर अनी, एक और नियंत्रण से बाहर चरित्र है। मैं तुमसे वैसे ही प्यार करता हूँ जैसे हम अपने बड़े भाई से प्यार करते है।

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宝贵如同碧玉。

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فرشته یک ومانند مهربان العاده فوق شما تحسینمیکنم. دادید انجام دیگران برای که کاری هر
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