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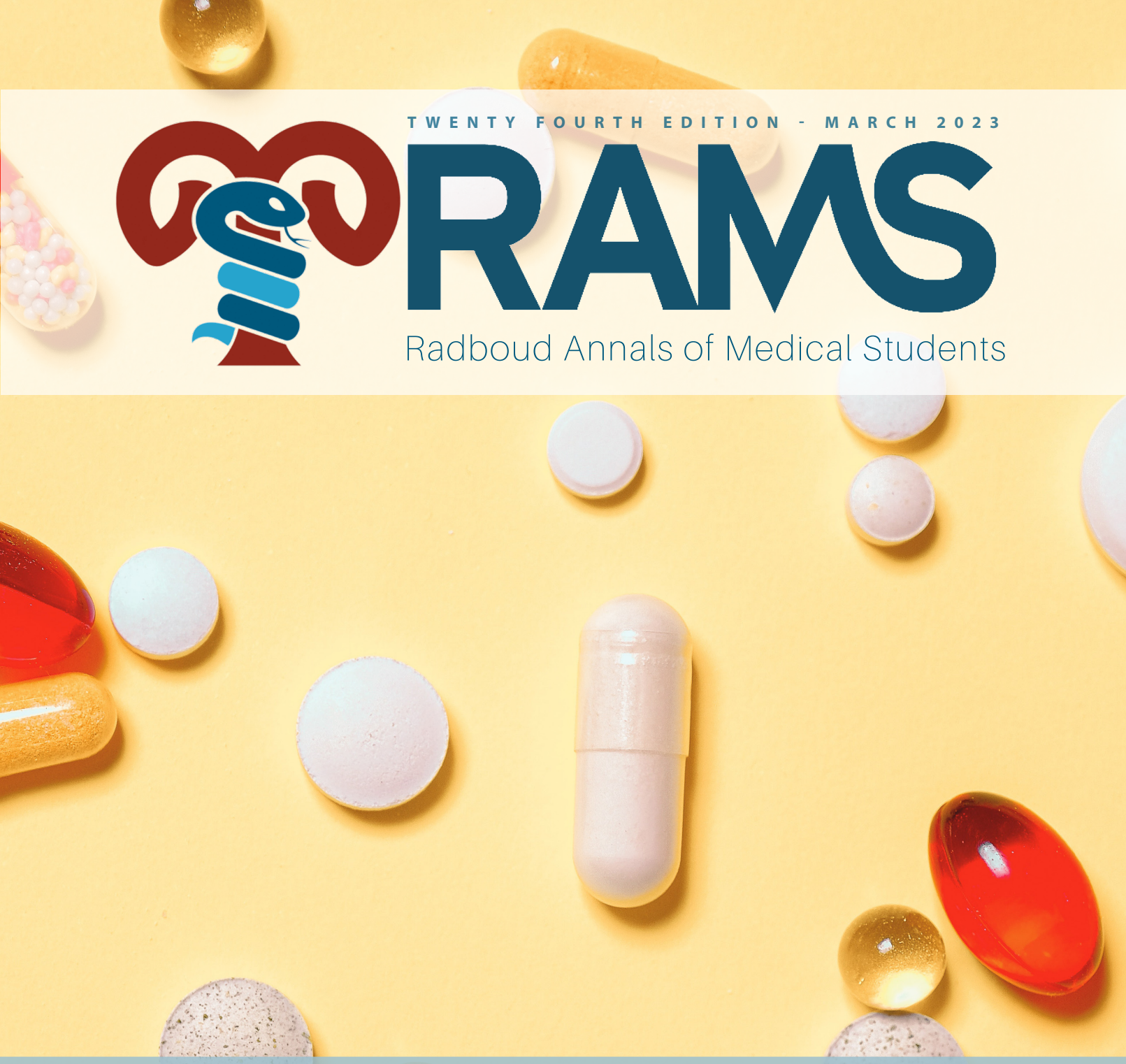

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FROM THE EDITORIAL BOARD

Dear reader,
Thank you for reading our 24th edition, the first edition of 2023. As always, the whole team of RAMS has worked hard to collect, process, edit and design the most interesting articles related to the field of medicine and biology. I will highlight a few of them here.

Who has never heard their parents or grandparents sigh and say 'everything was better in the past'? Often they refer to easier times, with less technology and a kinder society. But: does this vision reflect reality, or is it simply not true? In the Myth or Science article, this topic is discussed by Minke Holwerda. Are we humans truly less happy than we were 50 or 100 years ago? Are the seemingly rising numbers of depression cases related to our diet, busy working life and lack of exercise? Minke provides a balanced overview of studies related to this topic, and suggests possibilities to live a happier life in modern society. Read more on page 8!

I like to think that science is always evolving and improving, providing new insights into fields of medicine, chemistry, physics, biology and many more. However, I doubt that there will ever be a time when we can say: 'That's it. We've found the last piece of the puzzle.' In his column, Guus Brand describes the trend in science to look for a 'theory for everything', a grand truth to describe the world and to answer all questions. To see if Guus believes that such a theory exists, I would like to refer you to page 21.

Biomedical students Vera and Mies submitted their mini-review for publication in this edition. They explain the story behind the discovery of the relation between a symptom of autism spectrum disorder and a certain protein involved in neurotransmission, SHANK3.

I would like to invite all (bio)medical students of Radboud University to consider submitting their research article, review or another suitable text to the Editorial Board. We can provide guidance with improving your article, and it would boost your scientific writing experience. Maybe you will see your work printed in the next edition!

We hope you enjoy reading the 24th edition!

On behalf of the ninth board of RAMS,

Emma Vermeulen
Scientific Editor-in-Chief of the IXth Editorial Board

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ZEBRAS OF MEDICINE:
PROVIDING PROPER CARE FOR PATIENTS BY ACCURATELY DISTINGUISHING BETWEEN EHLERS-DANLOS SYNDROME AND FIBROMYALGIA

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Abstract

Ehlers-Danlos syndrome (EDS) and fibromyalgia (FM) are two syndromes that are largely misdiagnosed and underdiagnosed. A lack of readily available tests and poor awareness of both disorders among medical professionals make patients greatly reliant on the ability of a clinician to recognise EDS or FM. While patients present with similar symptoms in both syndromes, including chronic pain, fatigue and depression, facets such as hypermobility should raise suspicion for EDS in a clinician. The rise in evidence for EDS and FM as comorbidities further complicates this story. This review outlines the difficulties clinicians face in diagnosing EDS and FM. It aims to provide an overview of the differences and similarities between EDS and FM in terms of clinical presentation, diagnosis, and treatment options. Elucidating these could contribute to improved care and treatment for both patient groups.

Introduction

Ehlers-Danlos syndrome (EDS) is a broad term for a group of heritable disorders affecting the connective tissue [1]. Classically, these disorders are mostly characterised by hypermobility of the joints and hyperextensibility of the skin. However, other symptoms such as extreme fatigue, chronic pain, cardiovascular symptoms, gastrointestinal problems, and neurological issues also often present themselves [1]. While 13 subtypes of EDS exist, the most enigmatic subtype is hypermobile EDS (hEDS). With a prevalence of 1 in 10000 to 1 in 15000, hEDS is considered the most common form of EDS, which is estimated to affect 1 in 5000 individuals [2]. In contrast to the other 12 subtypes, hEDS is not yet associated with specific genetic mutations. Therefore, hEDS is only presumed to be heritable, and it is actually classified as a multi-faceted disorder based on clinical characteristics. Additionally, EDS patients experience a wide range and onset of symptoms [2]. Because of this, the diagnosis of EDS is appreciably complicated for many patients.

This difficulty in diagnosing EDS presents itself in many ways. On average, patients have to wait 14 years for an accurate diagnosis, at least in part due to poor awareness of the condition amongst medical professionals [3, 4]. This average is highly skewed by female patients, whom doctors on average take 16 years to diagnose with EDS, compared to 4 years for male patients [4]. Women are likely diagnosed later because their symptoms are written off as common complaints or psychological issues [4]. Additionally, 56% of EDS patients received at least one misdiagnosis before their correct EDS diagnosis. Having a misdiagnosis also increases the time to reach a correct EDS diagnosis from 8 years to about 20 years [4]. One patient describes her experience as follows:

> One day I counted that I had received 32 incorrect diagnoses before the correct one. They ranged from "you have nothing" to "it's all in your imagination" to very severe ones, like cancer. Some doctors told me I could live a normal life, others told me I was going to die. ([4], p. 137)

One of the most prevalent misdiagnoses for EDS is fibromyalgia (FM). This is a common chronic pain disorder, likely affecting between 2 and 4% of the population [5]. Aside from widespread chronic pain, the primary symptoms include fatigue and cognitive difficulties. One study with 57 participants found that 26% of FM patients also fit the criteria for hEDS [6]. Additionally, hEDS may explain some or all of the symptoms that were previously assigned to FM. FM in itself is also an underdiagnosed disease, with as many as 3 in 4 patients remaining undiagnosed (data on file. Decision Resources report 2009. Pfizer, New York, NY). Many FM patients experience negative mental health outcomes as a result of the invalidation of others, which could be further exacerbated by the delay in FM diagnosis for many patients [7]. The time to reach an FM diagnosis averages 6.42 years, resulting in delayed treatment, decreased psychological health, and possibly sub-optimal care [8]. Many factors have been found to influence this delay, with comorbidities, the age of the patient, and the age of the physician being a few of them [8]. A survey of experienced physicians described that the majority of the physicians in question reported difficulties in diagnosing FM, with the main causes being inadequate training in and knowledge of FM [9].

As one can imagine, the tumultuous road to a diagnosis has severe consequences for EDS and FM patients. Prolonged feelings of hopelessness and isolation due to a lack of a proper diagnosis add to the psychological burden already imposed on patients due to their physical symptoms. Roughly 38% of EDS patients described harmful psychological consequences of the delayed diagnosis. Additionally, the delayed diagnosis was responsible for more general deleterious consequences in 86% of these patients [4]. A previous misdiagnosis in FM patients was associated with prolonged disease duration, possibly due to a delay in the correct treatment options [10]. Many commonalities exist between EDS and FM. However, a differential diagnosis is needed to provide proper treatment to patients. Therefore, this review aims to outline the differences and similarities between EDS and FM. Moreover, the possibilities of EDS and FM as co-morbidities will be briefly discussed and the treatment options for both disorders will be compared.

Zebras of Medicine providing proper care for patients by accurately distinguishing between Ehlers-Danlos syndrome and Fibromyalgia
- Robbin Kramer

Clinical presentation

EDS is a heterogeneous group of disorders with a common thread of symptoms, namely joint hypermobility, skin hyperextensibility and tissue fragility. However, the different EDS subtypes each also present with their own symptoms as classified in 2017 [1]. The presentation of the five most common and clinically relevant subtypes is summarised in Figure 1. Classical EDS is distinguished from other EDS-like disorders primarily by the presence of skin fragility, atrophic scarring, and soft "doughy" skin [11]. Classic-like EDS is comparable to classical EDS but is generally associated with mild muscle weakness instead of atrophic scarring [11]. EDS also contains two cardio-vascular subtypes, namely cardiac-vascular EDS and vascular EDS. Patients with these forms of EDS often experience progressive cardiac-valvular issues and arterial rupture at a young age respectively [11]. Lastly, hEDS generally presents with the least severe clinical symptoms of the subtypes, but severe skeletomuscular complications do occur [2]. Next to that, hEDS patients often suffer from extraarticular symptoms like fatigue, cardiovascular issues, bone mass issues, neurologic and spinal issues, psychological issues, and gastrointestinal symptoms [12]. These symptoms more often than not result in chronic pain problems in hEDS patients. While the frequency and degree of this pain vary, many hEDS patients report daily musculoskeletal pain [12].

Psychological aspects of all EDS types frequently include anxiety and depression [13]. The chronic pain that EDS patients experience, combined with the delayed diagnosis, likely contributes to this. One of the factors that complicates the recognition of EDS, and thereby can delay the diagnosis, is that hypermobility and flexibility are often confused. Hypermobility refers to the laxity of someone's ligaments that surround a joint, whereas flexibility refers to one's ability to lengthen muscles [14]. Unlike muscles, once ligaments are stretched, they cannot return to their original length. Hence, the problem with ligament laxity in EDS. Patients with hypermobile joints can actually present with muscle stiffness and muscle spasms due to the overactivity of the muscles to correct for the laxity in the joints [15]. Patients suffering from FM on the other hand, present with chronic widespread pain as their primary symptom. Here, chronic pain is defined as pain lasting more than 12 weeks despite treatment. Widespread pain is defined as pain in the axial skeleton, both above and below the waist and on both sides of the body [16]. Based on current literature, FM is thought to be the result of perturbances in the processing and regulation of pain in the brain [16-19]. Together with this widespread chronic pain, the other two primary symptoms of FM are fatigue and cognitive difficulties sometimes described as fibro-fog. As a result of the pain, other symptoms such as sleep disturbance, fatigue, concentration issues, and depression also frequently arise [5]. The sleep disruptions may result in abnormal neurotransmitter levels, further exacerbating the pain amplification [20]. Further key symptoms that could raise suspicion for FM in combination with the main triad include muscle tenderness, joint stiffness, and irritable bowel syndrome [19].

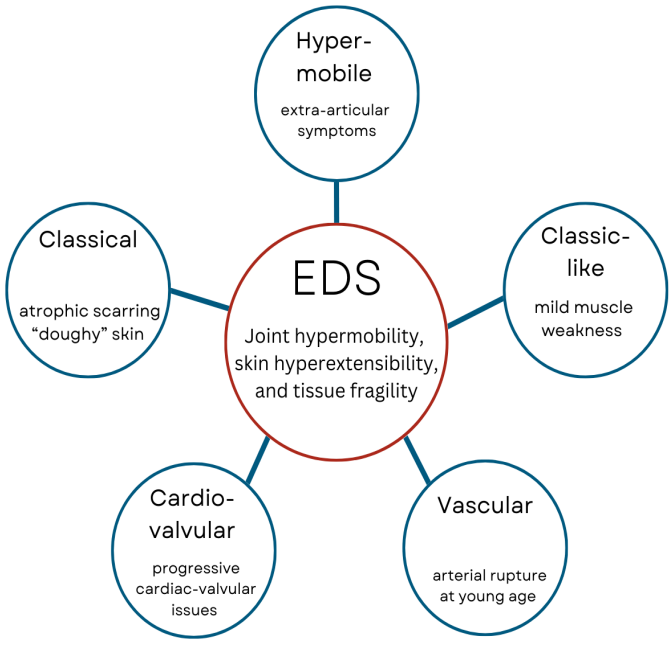

Figure 1 *- Overview of the clinical presentation of the most prevalent EDS subtypes.*

	Ehlers Danlos	Commonalities	Fibromyalgia
	Inherited connective tissue abnormalities	No definitive evidence yet	Hypersensitivity to pain
	Joint hypermobility, skin hyperextensibility, tissue fragility (subtype specific symptoms)	Widespread chronic pain, fatigue, anxiety, depression, GI issues	"Fibro-fog"
	Beighton score, exclusion of other joint hypermobility disorders, (genetic testing)	Systemic manifestation of symptoms	Pain location and duration, fatigue, "fibro-fog", symptom severity
	Genetic counseling	Multidisciplinary approach to manage symptoms	More vigorous exercise, antidepressants

Figure 2 *- A summary of the commonalities and differences between EDS and FM in terms of the cause of disease, clinical symptoms, diagnosis, and treatment. The FM diagnostic criteria of the 2016 version are presented here as it is more well known and commonly used than the 2018 criteria.*

The clinical presentation of EDS and FM overlaps quite a bit (see Figure 2). The key symptoms of FM can also be found in many EDS patients. Moreover, the pattern of autonomic symptoms, such as gastrointestinal, neuronal and spinal issues, is also very similar for EDS and FM [1, 19]. However, some differences in clinical presentations between EDS and FM should point a clinician towards the right syndrome. Hypermobile patients may counterintuitively present with muscle stiffness and muscle spasms. Although this can obscure the underlying issues of the patient, thereby complicating the clinical presentation of EDS, hypermobility should be a clear sign of EDS. Furthermore, the additional cardiovascular and scarring issues that are present in non-hEDS subtypes should assist a physician in making the distinction between EDS and FM.

Diagnosis

The diagnosis of EDS largely relies on the ability of a clinician to recognise the pattern of symptoms described above. Following a suspicion of EDS, further evaluation is needed to determine whether these are indeed consistent with EDS. This evaluation should focus on the extent to which the patient's body is affected by the possible underlying pathology [15]. Tests such as a CT scan, MRI or echocardiography can be used to further evaluate the effect of the underlying pathology [15]. Ultimately, the clinical diagnosis can

be verified using molecular screening for most EDS subtypes [11]. Apart from hEDS, all subtypes have been found to have a basis in one or more genetic mutations. Nonetheless, the absence of these confirmatory genetic results does not rule out an EDS diagnosis. Specific types of mutations are likely to go undetected by the current diagnostic molecular techniques [11]. Alternative diagnoses should certainly be reviewed in the absence of EDS-specific mutations.

However, hEDS is not so easily diagnosed, as it remains a fully clinical diagnosis without genetic confirmation. To be diagnosed with hEDS, patients need to simultaneously meet all three of the following criteria. First, they need to present with generalised joint hypermobility, as assessed by the Beighton score [11]. This test measures the mobility in five joints and assigns a score from 0 to 9 to the total hypermobility of the patient. Nevertheless, patients that score low can still score positively for joint hypermobility after consideration of other joints [11]. The Beighton score should be considered mostly as a diagnostic screening tool since factors such as age, stretching exercises and ethnicity affect joint hypermobility. The second criterion for hEDS is the presence of at least two of the following features: systemic manifestations of a more generalised connective tissue disorder; a positive family history in first-degree relatives; and musculoskeletal complications (e.g. musculoskeletal pain and recurrent joint dislocations in the absence of trauma) [11]. The last criterion requires the exclusion of alternative connective tissue disorders or other diagnoses that could include joint hypermobility (e.g. Marfan syndrome or skeletal dysplasias) [11]. Other symptoms are also abundantly present in hEDS but lack the sensitivity or specificity to be included in the formal diagnostic criteria. These include fatigue, gastrointestinal disorders, anxiety, depression and sleep disturbances [11].

FM used to be a diagnosis per exclusionem, meaning it could only be assigned to a patient if all other possibilities for a different diagnosis were exhausted [21]. Instead, the diagnosis is now based on a set of clinical criteria, similar to hEDS (Figure 2). One of the reasons for this is the current understanding that FM can and does co-occur with other chronic illnesses [5]. Many updates have been made to the diagnostic criteria for FM in the last three decades. The most recent criteria, established in 2018 and 2016, defined the core features of FM slightly differently. They both consider the duration and location of pain, but the 2018 version includes fatigue as a core feature, while the 2016 version assigns a score to the spread and severity of the pain symptoms [22, 23]. Additional features in the 2018 version that should point towards FM include but are not limited to generalised soft tissue tenderness, cognitive symptoms, and stiffness [22]. Opinions vary on whether these diagnostic criteria can fully capture the diversity in FM presentations, partly because of the diversity in this presentation and the large group of undiagnosed patients [24]. Diagnosis of FM is currently not supported by laboratory testing or imaging studies. Therefore, these tests should primarily be used to evaluate alternative diagnoses.

EDS and FM as comorbidities

Increasing evidence supports the presence of EDS and FM as co-occurring disorders. Multiple studies have reported an association between hypermobility and FM which is significantly above that caused by chance [25-29]. For example, 81% of FM patients had joint hypermobility and 40% of children with joint hypermobility had FM in a study of schoolchildren in 1993 [25]. Additionally, a study by Alsiri et al. found a 68%-88.9% prevalence of concomitant hEDS and FM diagnoses [30]. The two disorders are thought to co-exist due to their similar pathophysiology [31]. For instance, the central sensitisation that is thought to underlie FM likely amplifies the joint pain that results from hEDS. Moreover, hypermobility scores have also been found to significantly predict symptom levels in FM patients [32]. An explanation for this could be that joint hypermobility plays a role in the pathogenesis of chronic pain in FM. On the other hand, dysautonomia, a dysfunction of the autonomic nervous system, has also been proposed as a key link between FM and hypermobility. Both EDS and FM patients have higher frequencies of dysautonomia than the general population, and it has been proposed to be causal for some of the syndromes' symptoms [31]. However, the association between FM and EDS is still imperfectly understood [29]. Further research is needed to distinguish between misdiagnosed patients and patients with FM and hEDS as comorbidities.

Treatment options

Unfortunately, neither EDS nor FM is currently curable. EDS and FM treatment focuses on managing symptoms and limiting disease progression, thereby improving a patient's quality of life (Figure 2) [15, 33]. The primary treatment for EDS is physical therapy to strengthen the muscles and joints and prevent joint dislocations. Additionally, EDS therapy aims to manage the pain, fatigue and psychological symptoms experienced by EDS patients. Furthermore, blood pressure medication is prescribed to patients diagnosed with an EDS type with cardiovascular involvement to reduce stress on the cardiovascular system [15]. The pain patients experience in EDS is managed by the use of over-the-counter medication. Stronger painkillers are generally only prescribed for acute injuries [34]. Unfortunately, medical interventions are often only partially successful in treating FM. Therefore, much of FM treatment involves lifestyle changes, such as stress management, sleep habits, and a balanced diet [33]. The medications that are prescribed for pain relief include over-the-counter painkillers, antidepressants, and anti-seizure drugs. These drugs have the combined benefit of treating the depressive symptoms, as well as the sleep disturbances and pain of FM patients [33]. In both EDS and FM, patients are often provided with opportunities to acquire self-management skills to recognise and act on upcoming symptoms [15, 33].

A major risk of misdiagnosing a disease is harming a patient by giving improper treatments. Much of the lifestyle changes that are prescribed to manage symptoms are similar for EDS and FM, so this seems to pose less of a risk here. However, there is a notable difference in physical therapy regimens for both syndromes. Moderate to high–intensity aerobic exercises, such as yoga, Nordic walking or swimming, are well-tolerated by many FM patients and even recommended to reduce pain and depression and improve physical function [35]. However, while physical therapy for EDS patients includes strengthening exercises, these patients often experience a higher degree of exercise intolerance than FM patients [31, 36]. This intolerance can result in an exacerbation of symptoms in EDS patients due to exercise. Therefore, the proposed treatment for FM could aggravate EDS symptoms if a patient is incorrectly diagnosed and assigned the wrong treatment.

Conclusion

As both FM and hEDS suffer from severe underdiagnosis and misdiagnosis, a proper understanding of these two disorders is essential. The differential diagnosis of FM and hEDS is limited, but some characteristics can discriminate between the two disorders. Joint laxity and skin extendibility should alert a clinician to the possibility of one of the many subtypes of EDS. Both disorders are diagnosed by assessing a group of clinical symptoms, which underlines the essentiality of sufficient physical examination and

history taking. While treatment for EDS and FM overlaps as well, some pharmacological treatments are not to be used interchangeably for both disorders. What further complicates this story is the likelihood of analogous pathophysiology in hEDS and FM. In conclusion, further research is needed into the pathogenesis of hEDS and FM, as this might lead to more sensitive and specific diagnostics and treatment. As of now, more clinicians should be alerted by the clinical presentation of both hEDS and FM to start reducing the number of misdiagnoses and underdiagnoses in both disorders.

Acknowledgements

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MYTH OR SCIENCE? MODERN TIMES ARE CAUSING DEPRESSION

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Insight

It is a phrase often uttered: 'in the good old days, everything was better'. And after these last few years in the face of – just to name a few examples - a pandemic, war, and climate change, this statement might start to feel more and more true. Were we not happier in the past? Are these modern times and all its crises causing us to be more anxious and depressed? In this editorial, we will find out whether we really experienced fewer mental health problems in the good old days and what the reason for this might be.

Introduction

According to the World Health Organization, mental health conditions are on the rise and quickly becoming a large public health concern. They are even naming it 'a leading cause of disability worldwide' [1]. Generally speaking, research agrees with this statement.
Between 2007 and 2017, there was a 13% rise in mental health conditions and substance use disorders [2]. One study that investigated the change in the global burden of depression between 1990 and 2017, found an increase from 17.2 million incident cases in 1990 to 25,8 million in 2017 [3]. In the United States, rates of major depression rose from 3.33% to 7.06% between 1991-92 to 2001-2 [4]. A more recent study found an increase in major depressive episodes from 2.0% to 3.2% between 2010 and 2019 among older adults. [5] The Lundby study compared the prevalence of mental disorders between 1947, 1957, and 1972 and found a tenfold increased risk for depression among young adults from 1957 to 1972 compared to 1947-1957 [6].

It is good to realise that not all research finds evidence for increasing cases of depression. Other studies performed in Canada and the Netherlands found that depression rates remained stable. However, one should consider that depression rates remained stable, despite the substantial increase in investment in treatments [7-9]. As research on depression did not start until the 20th century, accurate knowledge on trends and prevalence of depression from earlier centuries is not available. Furthermore, research on depression from the 20th century also suffers from limitations, such as recall bias, but evidence from longitudinal studies generally confirms the increase in depression [10].

Keeping this in mind, depression might indeed be placed under the umbrella of 'diseases of modernity', where it is accompanied by, among others, diabetes, obesity, heart disease, and cancer [11]. But what is 'modernity' exactly, and why is it being held responsible for these conditions?

Modernity

To explain the concept of modernity, we must return to the time that came before 'modern' times. We are a long way from the lives lived by our hunter-gatherer forebears. Therefore, it is hard to believe that the hunter-gatherer lifestyle was prevalent for almost 99% of human history [12]. The agricultural revolution that significantly changed our human lifestyle 'only' happened 12,000 years ago.

This revolution meant a change from a nomadic and very active lifestyle to a more sedentary one. Over a few thousand years, we learned to farm and started living in settlements. Increased availability of food led to exponential population growth and subsequently to rising population densities, the hierarchisation of communities, control of natural resources, and an increase in armed conflicts [13].
In the late 1700s and early 1800s, the industrial revolution enters the scene and starts off the historical period of 'modernity': in Western Europe and North America, technical innovations allow for mechanization of agriculture and revolutionise our use of power, leading, once again, to significant social, cultural, and economic changes [13].
Although rapid urbanisation originally led to worse living circumstances, eventually improved civic hygiene, clean water supplies, sewage disposal, the emergence of public health infrastructure, more advanced medical technology, and the invention of vaccination decreased mortality, and increased life-span and population growth [13-15]. Another two industrial revolutions later, and we have arrived at the fourth industrial revolution of our current time. This time, it is exponential technological change, instead of just linear change [16].

An evolutionary mismatch

One of the consequences of these revolutions is the rise of non-communicable diseases (NCDs) as main cause of death [12]. The increased prevalence of NCDs is often explained by the 'evolutionary mismatch theory'. This theory proposes that due to rapidly changing environments following industrialisation, there is a mismatch between our evolved genetics and the environment we are currently living in [17]. In other words: our world and lifestyle changed too quickly for the human genome to adapt to it [18].

According to evolutionary mismatch theory, depression or low mood might have been a coping mechanism with adaptive advantages in our evolutionary past, but in our modern lifestyle, depression is over-induced [19]. Evidence for this can be acquired by researching groups of people that are still transitioning into a modern lifestyle.

For example, researchers studied the White Thai ethnic minority in Vietnam whose lifestyles incorporate both modern features and traditional features more associated with our evolutionary past. They found that common features of modernity, such as boredom, low income, and low levels of exercise were positively associated with psychological distress, whereas more traditional features such as enough sleep, higher levels of exercise, and access to resources like food by earning a sufficient income were negatively associated with psychological distress [19]. Another study researched the prevalence of depression among four groups of women in settings with different levels of modernisation and found that depression rates were lowest in the most traditional setting among rural Nigerian women, and highest in the most modern setting among urban residents in the United States [20].

So, what about modernity is mismatching in such a way that it is causing depression? It seems that common factors in hunter-gatherer lifestyles, such as living in a close-knit community with low levels of socio-economic inequality, engaging in plenty of physical exercise, and consuming a healthier, traditional diet are protective factors against depression. On the other hand, common factors in modernized lifestyles, such as social isolation, being overworked, lack of exercise, and increased socio-economic inequality, are risk factors for depression and stress [19, 21].

Diet, exercise and sleep

Although no 'one' diet was consumed by the hunter-gatherers, traditional diets seem to be higher in fibre, lower in glycaemic index, and more nutrient dense than food consumed in industrialised cultures [22]. As our society industrialised, technological advancements changed our way of food production and supply. The rise of supermarkets across the globe has had many benefits, but has also provided easier access to highly processed foods as these are more profitable [23]. Another important factor is the role of mass media and marketing as a driver of the shift in diet composition globally [22, 23]. Furthermore, the speed at which new products become part of global markets has also increased significantly [23]. The Westernised diet is generally high-fat, high-sugar, sodium-rich, and processed using synthetic food dyes, artificial sweeteners and flavour enhancers. This diet has been linked to chronic disease including depression [10].
In contrast, the Mediterranean diet conforms to a traditional dietary pattern and has been shown to improve physical health and quality of life [21]. One prospective study performed in 2009 found that the incidence of depression was lower among those that adhered to the Mediterranean dietary pattern [24].

In addition to our changing diets, exercise has declined. Exercise is crucial for regulating appetite, energy balance, and for the prevention and treatment of chronic diseases, including depression. [10, 21]. Where the hunter-gatherers were estimated to expend about 3,000 calories a day, surveys in the US show less than 50% manages to reach the recommended amount of physical activity [10, 21].

Not only have our indoor, sedentary jobs led to a decrease in physical activity, but they may also be to blame for widespread decrease in direct sunlight exposure. This may have resulted in our current vitamin D deficiency epidemic as well as widespread circadian rhythm dysregulation, which in turn could lead to changes in sleep patterns [10]. These changes may also contribute to an increased risk of depression [10, 25].

Urbanisation, nature & technology

A very important and unique element of modernisation is rapid urbanisation: in 1800, over 90% of the global population lived in rural areas. By 2050, over two-thirds of the global population will live in urban areas [26]. Another unique element accompanying this rapid urbanisation is the use of digital technology. Although the internet was not created until 1989, and social media not until the early 2000s, US adults now spend more than 6 hours per day on digital media [27]. Roger Walsh fittingly describes our current situation[28]:
'Yet today we are conducting a global experiment in which we increasingly spend our lives in artificial environments – walled inside and divorced from nature'.

As the experiment continues, we are slowly starting to understand the influence of technology and multimedia on our brain. In addition to many positive uses of digital technology, there are also substantial harmful effects: attention problems, such as symptoms of attention-deficit hyperactivity disorder (ADHD); impaired emotional and social intelligence due to less time being spent communicating face-to-face; technology addiction; social isolation; disrupted sleep and its previously described consequences; and may even adversely impact cognitive and brain development, resulting in, for example, poorer language development and behavioural problems [29].

The increased likelihood of developing depression might be linked to the use of mass media according to the 'social competition hypothesis' [30]. This hypothesis states that low mood is a mechanism that developed in our hunter-gatherer ancestors as a way to mediate competitive situations. More clearly explained: in situations of social competition, it might have been beneficial for individuals to enter in a temporary depressive state to accept defeat and accommodate reconciliation. However, in our current society mass media communication has allowed us to build social networks way beyond those of our ancestors. Therefore we are part of much larger – even worldwide – competitive groups that also include the most successful people on this planet. By constantly comparing ourselves to seemingly perfect 'competitors' on the other side of the planet, the depressive state that used to be beneficial is now over-induced. In modern research, there is some evidence that higher levels of screentime are associated with depressive symptoms among children [31] and that social media use is associated with depression in US young adults [32], but available research is conflicting [33].

Moreover, city-living has been clearly and extensively associated with an enormous range of mental health disorders, such as depression, alcoholism, and alienation [34]. In the meantime, we lack the positive influence on mental health that contact with nature brings us [35]. From an evolutionary perspective, our ancestors developed a connectedness to nature in order to survive. This is called 'biophilia' and this trait developed for the most part during a time only (wild) nature existed [36]. Only 0.1% of human history has been spent in urban environments, where nature is barely present or not at all. Therefore, our attraction and need to connect to nature is still present in our psychology, but this need is not met in many urban environments and may cause mental health problems [37] [38].

The modern social environment

Beyond diet, sleep, exercise and where we live, our social environment has also significantly changed. Pre-modernity and pre-industrialization, our hunter-gatherer forebears most likely lived in small-scale communities with strong interpersonal relationships and low social inequality [21].

Historically, industrialisation has always been considered a crucial factor in enhancing population health [15]. However, this may be an oversimplification as the direct consequences of rapid economic growth dramatically disrupt societies in terms of social relations and politics, as summarised in the four D's of rapid economic growth: disruption, deprivation, disease, and death [15].

Following industrialisation in the 1800s, traditional social structures characterised by a strong sense of community were replaced by a focus on individual needs that is present in our contemporary society [39]. Although individualism has been a great liberator and provided equal opportunities for many, we have also been made entirely responsible for our own successes and, unfortunately, failures [40]. Modern research in Canada has substantiated the importance of a strong community providing social support: a study researching depression and anxiety among both urban and rural dwellers found that those living in rural communities, associated with a strong sense of community, had a lower risk for depression. Disintegration is not just limited to larger communities; there is also evidence for the dissolving of family ties. This might play a role in the rise of depression rates [30].

A cross-temporal meta-analysis performed among American high school and college students between 1938 and 2007 found they scored above common cut-offs for psychopathology, including depression, five to eight as many times [41]. In addition to individualism, their results pointed towards materialism and unrealistically high expectations prevalent in Western culture as the culprits [41]. We are marketed to not only want to 'have' things, but also 'be' a certain thing, causing dissatisfaction with who we are [42]. Psychological studies have shown materialism to be associated with depression, anxiety, anger, isolation, and alienation [42].

In addition, Twenge et al (2009) also name the cultural shift away from intrinsic goals, such as finding meaning in life as a possible reason for a higher risk of psychopathology [41]. As society changed and scientific understanding expanded, religion and religious traditions that provided both answers and meaning in life decreased, exposing us to nihilism - the belief that there is no meaning to life at all [43]. One prospective study found that religiosity protected against depression and helped in depression recovery [44]. Religion provides meaning, hope and a supportive community; as long as the religious tradition does not hold its followers up to impossibly high standards and does not centre around themes of punishment and guilt [28, 45].

Modernity has even been proposed as a driver of narcissism [46]. We may have been so transformed by these social changes, that we have turned into the 'homo economicus', which is described as:
'…persons characterized by extreme individualism, lack of empathy for others and need for admiration to compensate for their fragile self-esteem… [46]'.
Thus, living in our capitalist, consumption-based Western society has brought good things, but is also characterised by competitiveness, social isolation, socioeconomic inequality, family and community disintegration, and war. This is making us more susceptible to depression [10, 42, 47].

Some nuance

It is obvious then, is it not? Our genes simply do not fit in these modern times and as a result, our chances of happiness grow ever slimmer with each passing year. The grass was much greener when we were still sneaking through it on the hunt for our next meal.

Yet, it is good to remember that we humans have the tendency to romanticise the past, while being overly pessimistic about our future [48, 49]. When asked whether people believed the world was getting better or worse, only 3% of people in high-income countries such as France and Australia gave a positive answer [49]. In the meantime, poverty, child mortality and violence are declining, our lives are longer and healthier, and, let us not forget, we have successfully survived numerous end-of-world predictions [49]. A paper on exhaustion even suggests that we have unjustly pathologised modernity [48]. After all, depression is nothing new. In fact, 'melancholia', from which our modern concept of depression originates, was already described by Hippocrates, who lived between 460 and 379 BCE [50, 51]. Similar to Schaffner's (2016) view on exhaustion, is depression not universally present throughout history and therefore simply part of the human condition [48]?
In addition, our increased awareness surrounding mental health and depression may also be in part responsible for the rise in depression diagnoses [30].

Conclusion

In conclusion, a genetic mismatch between past and current times is definitely a plausible explanation for modern health problems. However, nostalgia for a happier and simpler past is often misplaced and returning to our old ways is definitely not a solution. The fact remains that our world is changing rapidly and it is not always easy to keep up. However, as modernity has also supplied us with a wealth of knowledge at our fingertips, we are certainly equipped to incorporate the healthy elements of our hunter-gatherer past into our futures. And that, at least, is very positive.

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OMALIZUMAB AS AN OPPORTUNITY IN THE TREATMENT OF IGE-MEDIATED PEANUT PROTEIN ALLERGY

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Abstract

Immunoglobulin-E-mediated peanut allergy is one of the most severe and well-known food allergies in the western world. Current treatment consists of allergen avoidance and pharmacological intervention in case of accidental exposure to the culprit allergen. Patients with severe peanut allergies can receive additional allergen immunotherapy. While this therapy is generally effective at reducing the severity of allergic reactions, it takes a long time to reach effective levels. Additionally, its effects – while impressive – leave something to be desired as the level of tolerance is merely enough to prevent an allergic reaction from a small accidental exposure. Omalizumab, a biological used to treat other immunoglobulin-E-related diseases such as allergic asthma and spontaneous urticaria, could be used in the treatment of peanut allergy as well. While the theoretical background of omalizumab efficacy against peanut allergy is sound, few studies have looked into this opportunity. Three phase I/II studies and three phase II studies have thus far been performed, examining omalizumab as monotherapy, or as an add-on for peanut oral immunotherapy. Omalizumab as monotherapy appears to induce an estimated 50-fold increase in the maximum tolerated dose of peanuts with minimal adverse events. Omalizumab as an add-on for oral immunotherapy appears to be even more impressively effective. Using omalizumab as add-on therapy for oral immunotherapy, subjects were able to reach peanut protein maintenance doses up to six times higher in only one-third of the time compared to conventional oral immunotherapy. Whether this effect persists after omalizumab discontinuation is not fully clear. Thus far, the studies have included few participants and interstudy heterogeneity is high. As such, risk of bias in the data is high. However, omalizumab poses a hopeful opportunity for severely allergic patients, but more and larger studies need to be performed before clinical implementation for this indication can be considered.

Background

Food allergy

The prevalence of food allergies has been increasing steadily in the western world during the past century. Current estimates of prevalence range from 2 - 4% in adults, and up to 8% in children [1, 2]. While the epidemiological mechanisms responsible for the increase in prevalence are not fully clear, theories such as the hygiene hypothesis - the idea that reduced exposure to pathogens due to increased sanitary conditions in the western world results in the immune system recognising food proteins as dangerous - attempt to elucidate this effect [3]. Food allergies can be described as a collection of disorders in which the immune system reacts to a food component [4]. Food allergies are distinctly different from food intolerances, as the latter is caused by metabolic insufficiencies and generally does not include an immune component, while the former is dependent on the involvement of the immune system [4].

Food allergies can crudely be divided into three categories (Figure 1): immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed. This review will only cover IgE-mediated food allergies. IgE-mediated food allergies are type I hypersensitivity reactions. As such, these reactions can develop quickly following contact with the allergen. During a reaction, patients can experience symptoms in multiple organs, including the skin, gastrointestinal tract, lungs, and circulatory system, as well as severe systemic conditions such as anaphylaxis. Food-induced anaphylaxis is a serious, life-threatening reaction, which requires immediate administration of intramuscular adrenaline as life-saving medication. Next to this, an IgE-mediated food allergic reaction can exacerbate other IgE-mediated diseases, such as allergic asthma.

Peanut protein allergy is perhaps the most widely known form of IgE-mediated food allergy. IgE-mediated peanut protein allergy (IMPA) is a serious allergy, in which small exposures often lead to severe reactions, including anaphylaxis, in a matter of seconds to minutes after exposure. Due to its strict IgE-linked mechanism and societal infamy, IMPA is the most suitable form of IgE-mediated allergy to study for new discoveries.

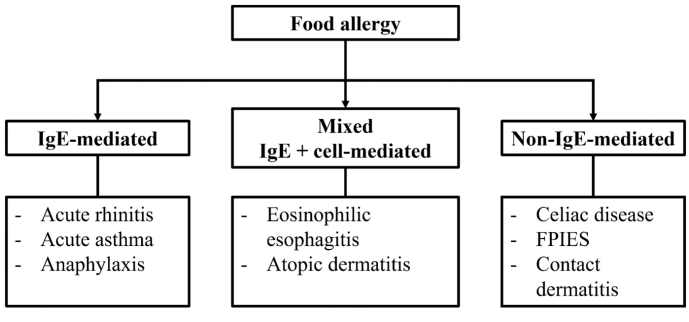

Figure 1: *Overview including examples of IgE-mediated, mixed, and non-IgE-mediated forms of food allergy. IgE - Immunoglobulin E; FPIES – Food-Protein Induced Enterocolitis Syndrome.*

Immunological processes in IgE-mediated food allergy

IgE-mediated food allergies are closely associated with other diseases in which IgE commonly plays a role, such as allergic asthma, atopic dermatitis, and allergic rhinitis. These diseases are frequently found together, as they employ a similar mechanism of action [5]. Type 2 helper T-cells (Th2) are significantly involved in all atopic diseases and form the basis for later reactions. Food allergy consists of a sensitisation phase and an effector phase. During the sensitisation phase, the subject first encounters the allergen (Figure 2) [4]. While it is not fully clear why only some exposures will lead to food allergies, it is suggested that barrier dysfunction (e.g., lung/gut epithelium) is likely involved [4]. The skin-gut axis also plays an important role, as sensitisation to an allergen in the skin can cause symptoms upon allergen challenge in the gastrointestinal tract [6].

In a healthy gut, macrophages sample food allergens and transport these across the gut membrane. Here, the sampled allergens are presented to dendritic cells, which present the allergen to naïve T-cells in the context of anti-inflammatory factors. The naïve T-cells differentiate into allergen-specific regulatory T-cells. Regulatory T-cells promote allergen tolerance. In the case of disrupted barrier function, food allergens can pass the gut membrane without being cleaved or sampled and are instead found by dendritic cells directly. Additionally, the damaged epithelium releases pro-inflammatory cytokines which expand and activate type 2 innate lymphoid cells and promote the polarisation of naïve T-cells towards a Th2 response [4]. Innate lymphoid cells and Th2 cells subsequently secrete cytokines promoting the recruitment and proliferation of basophils and eosinophils. Furthermore, B-cells are recruited and differentiated to produce food-allergen-specific IgE [4, 7].

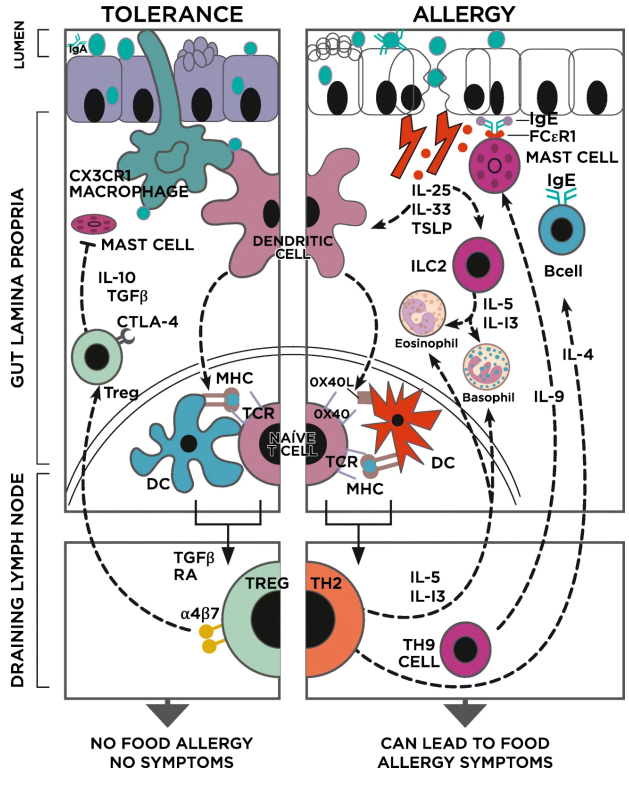

Figure 2: *Comparative overview of the mechanisms of tolerance and allergy in the gut. Figure adapted from Anvari et al. (2018) [4]. On the left, the normal (tolerant) situation is depicted. The immune system promotes tolerance towards sampled food allergens through a series of anti-inflammatory events. On the right, a damaged epithelium induces the allergenic sensitisation process. Through a host of pro-inflammatory events, tolerance to the food allergen is lost and allergen-specific IgE is formed. This allergen-specific IgE is found free in the circulation, as well as bound to the FcεRI receptors on mast cells, ready to induce an allergic reaction upon exposure to the food allergen. Abbreviations: IL – Interleukin; MHC – Major Histocompatibility Complex; TCR – T-cell receptor; DC – Dendritic Cell; Treg – T regulatory cell; IgE – Immunoglobulin E; TGF-β – Transforming growth factor β; TSLP – Thymic Stromal Lymphopoietin.*

Following sensitisation, allergen-specific IgE can be found in the circulation. Upon exposure, IgE will bind the allergen and cross-link FcεRI - high-affinity IgE-receptors - on the surface of mast cells and basophils, causing degranulation and release of mediators into the circulation [4]. These mediators act on various organ systems and will lead to symptoms in a patient. Histamine release is one of the most important mediators in this process, causing vasodilation, increased heart rate, and glandular secretion. Other mediators, such as tryptase, leukotrienes, and prostaglandins, are involved in bronchoconstriction and increased vascular permeability, among others [4]. By doing this, they form a positive feedback loop to enhance the reaction. At sufficient concentrations, these mediators can cause a cardiovascular crash, close the trachea through swelling, or reduce lung flow, all of which can have a deadly outcome.

Current treatment

Effective treatment of IgE-mediated food allergies is currently lacking for all patients, but most notably for severely allergic patients. The mainstay of treatment consists of allergen avoidance. In addition to dietary intervention, allergy treatment can include pharmacological intervention (e.g., oral antihistamines) in case of a reaction. These two pillars of treatment are not sufficient for patients with severe IMPA. These patients would benefit most from a therapy that would reduce the allergic sensitivity or decrease the potency of allergic responses.

As a final pillar of allergy treatment, allergen immunotherapy can be used to reduce the severity or impact of the food allergy in patients with severe food allergies. Allergen immunotherapy involves exposing the patient to doses of allergen lower than their reaction threshold [8]. This process will slowly build up tolerance to the culprit allergen and increase the threshold dose for an allergic reaction to occur. Allergen immunotherapy can be given through various routes of exposure, such as oral (OIT), sublingual, and epicutaneous exposures, as well as subcutaneous injections. In the case of peanut allergy, OIT has shown the most impressive increases in sustained tolerance doses [9]. However, allergic reactions and adrenaline use as rescue medication are common during OIT [8]. OIT consists of a slow dose-escalation phase in which the patient is exposed daily to increasing concentrations of their allergen over the course of months, followed by an indefinite daily maintenance phase. While the goal of reducing the sensitivity to the culprit allergen may be achieved through OIT, the treatment will not eliminate the allergy. Patients must remain allergen-avoidant and remain on daily OIT to retain the built-up tolerance.

Biologicals in the treatment of IgE-mediated diseases

Therapies for other IgE-mediated diseases, similar in mechanisms of disease, have been developed in the biologicals class. Biologicals are products produced by living organisms and often have an immunomodulatory effect [10]. Due to the similarity in disease mechanism between IgE-mediated allergic diseases, these biologicals could be promising for use in the treatment of IMPA. One prime example of a biological that could be of interest in treating IMPA is omalizumab.

Omalizumab (brand name: Xolair; investigative ID: RG-3648) was approved for use in the EU in October 2005 [11]. It is currently indicated for use as add-on therapy in patients older than six years

with severe persistent allergic asthma. Additionally, it is used as an add-on treatment for chronic spontaneous urticaria and severe chronic rhinosinusitis with nasal polyps, in which antihistamines and corticosteroids, respectively, offer insufficient effects. Omalizumab is dosed using subcutaneous injections every two to four weeks, depending on the disease state [11].

Omalizumab is a humanised IgG1κ monoclonal antibody produced in a Chinese Hamster Ovary cell line. Omalizumab was constructed using DNA recombination and its antigen-binding fragment consists of human framework regions and murine complementary-determining regions. Omalizumab binds to an epitope in the Fc region of IgE and prevents binding of IgE to the high-affinity IgE-receptor FcεRI on basophils and mast cells. Additionally, omalizumab prevents binding of IgE to the low-affinity IgE-receptor FcεRII on the surface of B-cells. These mechanisms of action deplete free IgE and prevent or reduce the activation of the allergic cascade [11]. As a result, little to no effector cells are degranulated and mediators are not released into the circulation, preventing allergic symptoms upon allergen exposure. While the theory behind omalizumab efficacy is present, it remains to be seen what the effects would be in the clinic. Omalizumab could serve as monotherapy by depleting the IgE storage and thus prevent allergic reactions by taking away a key molecule in the cascade. Additionally, omalizumab could be used in tandem with OIT to reach much higher maintenance doses of OIT in a shorter time period. However, only a handful of phase I and II studies have thus far been performed for the use of omalizumab in peanut-allergic patients (Table 1).

Discussion

The use of omalizumab in the treatment of IMPA generally has insufficient reliable evidence to be regarded as sensible or not. High interstudy variability in methods and outcomes complicates the interpretation of the available evidence. Additionally, as omalizumab is a pharmaceutical product under investigation for possible new indications, some public trial reports appear intentionally vague or incomplete, further complicating the interpretation of available evidence. Although some studies show considerable potential for using omalizumab as monotherapy or add-on for peanut OIT, these drawbacks mean there is too little reliable evidence to form an informed recommendation.

Summary of available evidence

Omalizumab as monotherapy was examined in Trials I, II, and III (Table 1). Omalizumab monotherapy appears to significantly increase the threshold dose for a peanut-induced allergic reaction, showing this effect following only a few doses of omalizumab in adults aged 18-44 [12]. In adolescents aged 12-19, it was shown that individualising the doses of omalizumab based on the *in vitro* reactivity of basophils may enhance omalizumab monotherapy efficacy [14]. Omalizumab administration appears to be safe, with reported adverse events generally only concerning allergic symptoms upon peanut challenge. Due to a high risk of bias in these trials, the quality of evidence is very low. Trials I, II and III included a limited number of participants (14, 11, and 23). None of the trials used placebo arms. Additionally, the food challenge in Trial III was not blinded, while Trial II did not include any experimental peanut exposure [13, 14]. All three trials used different symptom-scoring systems. None of the trials corrected for multiple comparisons, resulting in a likely overestimation of significance. Furthermore, none of the trials appear to be powered for their primary outcome, meaning too few participants may have been included to properly detect effects in the primary outcome. Moreover, the trial application of Trial I suggests all nine measured outcomes are primary outcomes [12]. Due to the low number of participants, non-overlapping ages, dosages, and study setup, the available evidence is of insufficient quality to either recommend or not recommend omalizumab monotherapy as a treatment for IMPA.

Omalizumab as an add-on treatment for peanut OIT was examined in Trials IV, V, VI, and VII, and appears to be promising [Table 1]. Peanut OIT by itself has a desensitisation rate of 68% following 24-52 weeks of treatment, with 76% of treated subjects able to safely ingest (i.e., without an allergic reaction) 300 mg peanut protein (approximately one peanut kernel) and 56% of treated subjects able to safely ingest 1,000 mg peanut protein [8]. Adding omalizumab to OIT appears to reduce the time needed to reach the maintenance phase and allow for higher maintenance doses. However, the effect may decrease following omalizumab discontinuation [Table 1; 15, 18, 19]. The efficacy results are consistent across trials and are higher than the reported tolerated doses and time-to-effect of OIT monotherapy in the literature [8]. The long-term effects of omalizumab as an add-on therapy for OIT are unknown. One trial attempted to look at the long-term effects of omalizumab-initiated OIT, but due to high intra study heterogeneity in the method of OIT and the dosing regimen, the study was disregarded [20].

Adverse event rate varied from 1-3% per dose, which is higher than reported for OIT monotherapy in literature [8]. This increase in adverse event frequency is likely due to the much higher doses of OIT compared to OIT monotherapy.

The quality of the evidence from the included trials is low, mostly limited by risk of bias as a result of study designs and small sample sizes. Most trials only included a small number of participants receiving omalizumab. However, the population is fairly consistent between trials, with all trials reporting on omalizumab in children and adolescents. Three trials used a single-group, open-label treatment study design, while only one trial used a double-blinded, placebo-controlled study design. None of the trials appeared to correct for multiple comparisons, even though paired measurements at different time points were compared. While the body of evidence must certainly be expanded before omalizumab can find widespread use in the clinic as an add-on treatment for peanut OIT, it seems omalizumab can enhance the efficacy and shorten the time-to-effect of peanut OIT. As such, omalizumab as an add-on treatment for OIT cannot be wholeheartedly recommended at this moment, but as the body of evidence grows, it is expected that trust in this treatment will grow. Phase III and IV trials (NCT03881696; NCT04037176; NCT03881696) examining the use of omalizumab as an add-on for OIT are currently recruiting subjects.

Final remarks

Omalizumab may have a place in food allergy treatment, helping those with severe peanut allergies quickly build a small tolerance to their allergen as monotherapy or peanut OIT enhancer. This small tolerance can mean the difference between generalised anxiety stemming from the fear of even the smallest accidental exposure, to a normal diet with reasonable allergen avoidance. While omalizumab is not ready to be used in the treatment of peanut allergy as is, the supporting evidence forms a suitable base of knowledge to justify studying its potential in the treatment of peanut allergy in future, larger trials.

Trial NCT	Study phase	Study design	Number of subjects	Age range	Type of	Primary outcome(s)	Most important findings
NCT00949078 (Trial I) [12]	Phase II	OL, SG	14	18 - 44	Monotherapy	Kinetics of clinical response to omalizumab treatment; association between clinical improvement and allergic effector cell suppression	Strong, sustained increases in median threshold dose during open food challenges from 80 mg peanut protein (n = 14) before treatment to 6,500 mg after 8 weeks of treatment (n = 13, p = 0.002) and 5,080 mg after 6 months of treatment (n = 10, p = 0.005 compared to pre-treatment).
NCT00382148 (Trial II) (unpublished) [13]	Phase II	OL, SG	11	Unclear (inclusion criteria: 6 - 75)	Monotherapy	Serious adverse events over the course of 52 weeks of omalizumab treatment	No serious adverse events were associated with the use of omalizumab.
NCT02402231 (Trial III, IV-I, IV-II) [14-16]	Phase II	OL, SG	23	12 - 19	Monotherapy (III); add-on for OIT (IV-I, IV-II)	Trial III: Suppression of allergic reactions to peanuts following individualised dosing regimens of omalizumab Trial IV-I: Peanut OIT of daily 2,800 mg for 12 weeks after omalizumab discontinuation and passing a 2,800 mg open challenge Trial IV-II: Immunological effects of omalizumab treatment	Trial III: 15/23 subjects needed higher dosing of omalizumab to suppress a predictive basophil variable; median tolerated peanut protein dose increased 50-fold following omalizumab treatment (n = 14, p < 0.001). Trial IV-I: all subjects reached 2,800 mg maintenance dose in median 10 weeks of OIT + omalizumab treatment; 48% of subjects pass a 2,800 mg open challenge 12 weeks after omalizumab discontinuation. Trial IV-II: treatment skews cytokine profile towards a Th1 phenotype. No significant effect on Tregs was observed.
NCT00932282 (Trial V) (main results unpublished; partial publication) [17]	Phase I/II	OL, SG	13	12 - 19	Add-on for OIT	Response to a 10,000 mg peanut protein challenge 11 or 23 months after omalizumab discontinuation	Two cases of eosinophilic esophagitis, likely caused by OIT; 3/7 subjects in the 11-month group and 1/6 subjects in the 23-month group were able to safely ingest 10,000 mg peanut protein 2-4 weeks after stopping OIT.
NCT01290913 (Trial VI) [18]	Phase I/II	OL, SG	13	8 - 16	Add-on for OIT	Rush desensitisation to 250 mg peanut protein without symptoms	12/13 subjects reached a 2,000 mg maintenance dose after 8 weeks of omalizumab treatment; All of these subjects safely completed a 4,000 mg cumulative dose DBPCFC 12 weeks after omalizumab discontinuation.
NCT01781637 (Trial VII) [19]	Phase I/II	DBPC	36 (8 placebo)	7 - 19	Add-on for OIT	Tolerance to 2,000 mg peanut protein 6 weeks after omalizumab discontinuation	23/29 omalizumab-treated subjects passed the 2,000 mg open challenge 6 weeks after treatment cessation versus 1/8 in the placebo group (p < 0.01); 22/29 omalizumab-treated subjects vs 1/8 placebo-treated subjects passed a 4,000 mg open challenge 12 weeks after treatment cessation (p < 0.01).

Table 1: *Overview of publications and trials identified through the PubMed search and included in the analysis. One peanut kernel contains approximately 300 mg peanut protein. Abbreviations: OL – Open-label; SG – single group; OIT – oral immunotherapy; Tregs – Regulatory T-cells; DBPC – double-blinded, placebo-controlled; DBPCFC – double-blinded, placebo-controlled food challenge*

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SHANK3 AND HYPERSENSITIVITY:
THE KNOWN AND THE UNKNOWN

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Abstract

Autism spectrum disorder (ASD) is a very heterogeneous neurodevelopmental disorder on both the genetic- as well as- clinical level. Hyper- and hypoactivity are clinical symptoms commonly seen in ASD patients; affected individuals can respond extremely, either too much or too little, to sensory stimuli. Genetically, ASD has been associated with numerous risk genes, however, one gene has been found to be frequently correlated with hypersensitivity in ASD patients: *SHANK3*. This gene on chromosome 22 codes for the SHANK3 protein that is part of the postsynaptic density (PSD) in which it regulates proper synaptic transmission and thus proper signalling between neurons. It is thought that SHANK3 is mechanistically associated with altered sensory perception. In this review we outline the current knowledge on the gene-to-function correlation between *SHANK3* and the clinical symptom of hypersensitivity.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction, as well as repetitive patterns of behaviour, activities, and interests, present from childhood [1,2]. The prevalence of ASD is estimated to be around 1% although in the Netherlands no quantitative research based on registered diagnoses has been performed [3,4]. Within the diagnosis of ASD there is a wide range of manifestations and severeness of the disorder. This is due to the heterogeneity of the disorder, on both the phenotypic level as well as on the level of the underlying cause. There is consensus on the pathogenesis of ASD, which states that the deficits found in ASD seem to be mainly caused by genetic mutations, leading to developmental alterations in neural connectivity [3,5]. It is found that these genetic mutations can be both inheritable and de novo mutations, and are mostly heterozygous [6,7].

Atypical behavioural responses to sensory information, defined as "hyper- or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment", is one of the impactful and commonly seen symptoms of ASD 1. Abnormalities in sensory sensitivity can possibly lead to abnormal social behaviour and difficulties in daily life. Also, sensory hypersensitivity might play a role in the presence of other ASD-related symptoms, such as learning disabilities, anxiety, attention- and sleep deficits, and hyperarousal [8,9].

Incorrect synaptic transmission is one of the factors that might play a role in sensory hypersensitivity and can be caused by genetic mutations. One of the heterozygous mutations found in ASD leads to a malfunctioning of the SH3 and multiple ankyrin repeat domains 3 (SHANK3) protein. SHANK3 is a postsynaptic scaffolding protein that – together with other proteins – facilitates correct synaptic transmission and development [10,11]. Current literature implies SHANK3 as a risk gene that has been associated with approximately 1% of the non-syndromic ASD patients [12]. Different types of mutations in SHANK3 can be found, relating to different phenotypic outcomes. For instance, some mutations lead to irregular dendritic spine formation of neurons while other mutations lead to a reduction in mGluR5 receptors, which play a role in neurotransmission [13].

SHANK3 contributes to synaptogenesis and proper synaptic transmission. Therefore, it has an impact on the stimulus transmission between neurons, and has a potential correlation to hypersensitivity in which proper synaptic transmission is affected 3. Whether and how the SHANK3 protein and hypersensitivity in ASD are correlated to each other has yet to be determined. Therefore, in this mini-review, we investigate what role SHANK3 plays in hypersensitivity in individuals with ASD.

SHANK3 and the postsynaptic density

The synapse of the postsynaptic excitatory neuron contains several structures to regulate proper neurotransmission (Figure 1). The postsynaptic membrane can contain voltage- and ligand-gated ion channels, and metabotropic receptors to facilitate neurotransmission. Another structure that is part of the synapse is called the postsynaptic density (PSD), which is a dense structure beneath the postsynaptic membrane. Scaffolding proteins in the PSD connect the ion channels and receptors in the postsynaptic membrane to each other, to other membrane components such as adhesion molecules, and to the actin cytoskeleton [14]. A major role for the PSD proteins is to anchor glutamate receptors such as AMPA and NMDA receptors to the postsynaptic membrane [15]. Proper functioning of the hierarchical cascade of scaffold proteins is needed to facilitate neurotransmission, as well as formation, maturation, and maintenance of the synapse [14].

SHANK3, encoded by *SHANK3*, is a synaptic scaffolding protein that can be found in the core of the PSD of excitatory neurons, which thus plays a role in connecting neurotransmitter receptors, ion channels, and other membrane proteins to the actin cytoskeleton or signalling cascades. Each part of SHANK3 has its own protein-protein connection and therefore contributes differently to the regulation of neurotransmission and synapse development. The six ANK repeats make interactions with the actin cytoskeleton, while the SH3 domain interacts with tyrosine kinases, which are part of signalling cascades in the postsynaptic neuron [10,17]. SHANK3 also anchors AMPA- and NMDA- glutamate receptors and metabotropic

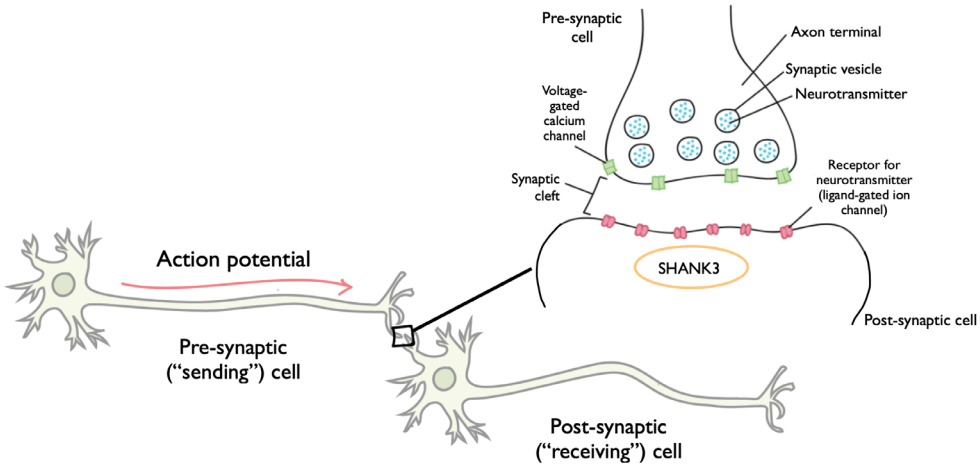

Figure 1: Neuronal cell showing factors contributing to chemical synaptic transmission between two neurons. Location of SHANK3 in the postsynaptic neuron is shown. Figure modified from Khan Academy, 2016 [16]

receptors to the postsynaptic membrane, which is important for chemical synaptic transmission and synapse development (Figure 2) [17,18]. Furthermore, SHANK3 also makes connections with other scaffolding proteins to interact indirectly with receptors, signalling molecules, and the actin cytoskeleton [17].

As SHANK3 has so many different and important functions in the PSD, the protein is often described as the "master regulator" of glutamatergic synapses [15].
Since SHANK3 plays such a fundamental role in coordinating the function and development of excitatory synapses, it seems logical that mutations in SHANK3 impair glutamatergic synaptic structure and function [19].

The history of *SHANK3*

At the tip of chromosome 22 lies the locus for *SHANK3*, more specifically in the 22q13 region. *SHANK3* and its association with ASD go back as far as 1985. However, at that time, scientists did not know it was specifically *SHANK3* that played a part in this. It all started with chromosome 22 instead, as Watt et al.[20] reported the first case of monosomy (absence of one member of a pair of chromosomes)

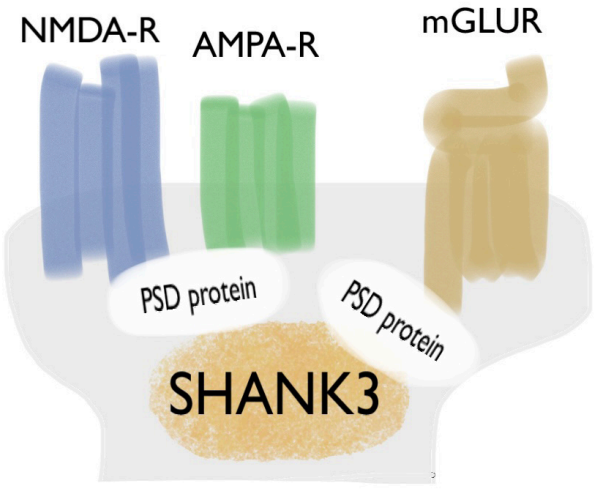

Figure 2: *SHANK3 function in the postsynaptic neuron where it, together with other PSD proteins, binds to the postsynaptic receptors to regulate chemical synaptic transmission.*

for the distal long arm of chromosome 22, currently known as the location for *SHANK3*. The 14-year-old male had developmental delays and absence of speech, features that are currently part of the clinical phenotype of ASD.
In 2001, the discoveries continued when Phelan et al.[21] described features of multiple individuals with a deletion in a specific region of chromosome 22, namely 22q13. The research group compared the reported clinical phenotypes to the features of individuals previously described in the literature. Symptoms such as developmental delay, delayed speech, and hypotonia were commonly present in both groups. Later that year, Bonaglia et al.[22] also described similar features for a 4.5-year-old male with a de novo translocation between 12q24.1 and 22q12.
Scientists unravelled the correlation between *SHANK3* and chromosome 22, more specifically the 22q13 region. Throughout the years, this location has been associated with several similar clinical phenotypes; therefore, it was suggested that a disruption of *SHANK3* could be responsible for several phenotypic features of 22q13.3 deletion syndrome.

Two years later, in 2003, *SHANK3* was identified as the most likely candidate gene for the neurodevelopmental and behavioural impairments in individuals with 22q13.3 deletion syndrome. To date, 22q13 deletion syndrome is known as Phelan-McDermid syndrome (PMDS). It is characterised by developmental delay, hypotonia, delayed development of speech, and autistic behaviours [23]. *SHANK3* mutations have also been identified in non-syndromic ASD, also known as classic ASD [24-26].
As mentioned before, SHANK3 has been associated with approximately 1% of non-syndromic ASD patients [12]. This includes mostly de novo *SHANK3* deletions or mutations, together referred to as SHANK3-deficiency. The loss of one copy (haploinsufficiency) of *SHANK3* is sufficient to cause neurobehavioral symptoms as seen in ASD [27]. Typical behavioural phenotypes like abnormal social behaviour and elevated anxiety, are found in SHANK3-deficient animal models. These characteristics resemble clinical features seen in human ASD patients. Furthermore, altered PSD levels of NMDA and AMPA receptors are also present in SHANK3-deficient animals, which is in line with the previously mentioned function(s) of SHANK3 [11,28-30].

SHANK3 and hypersensitivity

Hyposensitivity and hypersensitivity are common features of both PMDS patients as well as non-syndromic ASD patients [31]. These

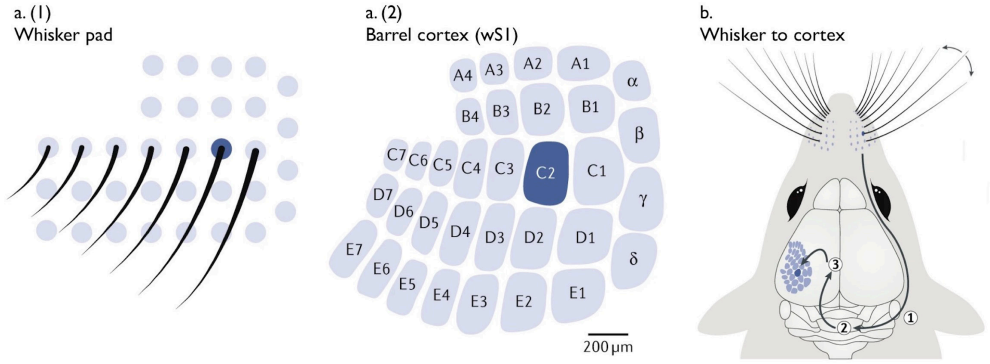

Figure 3: *a) Barrel cortex in S1, every whisker is represented by a specific region in the barrel cortex. Dark blue area around the whisker correlates to the dark blue area in the barrel cortex.*
b) Trajectory from an individual whisker to the thalamus to the barrel cortex in S1.
Figure modified from Petersen., 2019 [38].

individuals, with *SHANK3* mutations, often show an increased pain tolerance and aberrant tactile sensitivity [27]. This led to the suggestion that SHANK3-deficiency may also be correlated with abnormal sensory function in individuals diagnosed with ASD.
To investigate this hypothesis, rodent studies were used as it is to some extent ethically approved to alter the gene expression of rodents. Most studies on SHANK3-deficient mice have been focused on nociception – pain perception. Multiple research groups have reported hyposensitivity to painful stimuli in SHANK3-deficient conditions [32-35].
On the other hand, somatosensory function abnormalities, such as physical touch, have been little investigated in SHANK3-deficient mouse models. Chen et al. [36] were the first research group to investigate this by performance of a vibrissae (whiskers) motion detection task on SHANK3-deficient mice.
The researchers focused on the vibrissae since the neural trajectory from the vibrissae to the brain is well-defined. Fibres from a specific nucleus (ventral posteromedial nucleus) in the thalamus project specifically to the barrel region (representative sensory location of the whiskers) of the primary somatosensory cortex (S1) [37]. The S1 has a somatotopic map where each whisker is represented as a barrel which allows for precise activation of each whisker (Figure 3) [38].
During the task, an individual whisker was stimulated with different electrical intensities. The mouse was taught to lick his paws when he could detect, thus feel, the electrical shock. SHANK3-deficient mice licked their paws more often to weaker electrical stimulation than wild type mice without a SHANK3-deficiency. This suggests that a SHANK3-deficiency is associated with increased sensitivity to physical touch, also referred to as hypersensitivity.Chen et al. [36] also investigated the underlying neural mechanism of hypersensitivity in the SHANK3-deficient mice by performing calcium imaging on the neurons in the barrel region of S1. Calcium imaging relies on the calcium concentration inside the presynaptic terminal after an action potential (AP) has depolarized the synapse. Calcium in the presynaptic terminal controls the release of neurotransmitters, and therefore the firing activity between two neurons [39].
After the whisker was stimulated with a set electrical intensity, the calcium concentration inside the neurons of the corresponding barrel region was measured. Glutamatergic excitatory neurons of the SHANK3-deficient mice showed an increased firing pattern compared to the wild type mice. While the GABAergic interneurons of the SHANK3-deficient mice showed a decreased firing pattern compared to the wild type mice.
The altered excitatory and inhibitory neural activity in the SHANK3-deficient mice comes as no surprise. Many neurodevelopmental disorders such as ASD, epilepsy, and intellectual disability have been associated with an excitatory versus inhibitory imbalance, as it is thought to contribute to the pathophysiology of these types of disorders. Normally, excitatory and inhibitory neurons work in harmony where excitatory neurons activate the inhibitory neurons, and inhibitory neurons keep the excitatory neurons from firing too strongly. In neurodevelopmental disorders, however, a disturbed excitatory versus inhibitory balance usually means reduced activity of inhibitory neurons which leads to reduced inhibition of excitatory neurons, hence overexcitation [40,41].
The current theory states that SHANK3 expression is probably reduced in excitatory neurons of individuals with SHANK3 mutation(s). Since decreased expression of SHANK3 leads to reduced activity of the excitatory neurons, it cannot properly activate inhibitory neurons as it would normally do. As previously mentioned, inhibitory neurons attenuate the firing activity of excitatory neurons. However, as the inhibitory neurons are hypoactive, the excitatory neurons are overly active leading to overexcitation, which is thought to underlie the hypersensitivity in SHANK3-deficient mice [36].
Overall, these findings provide evidence that SHANK3-deficiency results in hypoactive inhibitory neurons causing decreased inhibitory control over excitatory neurons, hence hyperactivity.

Conclusion

Hypersensitivity is one of the most impactful symptoms commonly seen in ASD. Recently, *SHANK3* has been found to be of importance in the research on somatosensory hypersensitivity in ASD patients. According to the conducted research, a SHANK3-deficiency likely leads to decreased inhibitory control over the excitatory neurons, leading to an overexcitatory network in the brain, which is thought to underlie hypersensitivity. However, the research on *SHANK3* and its correlation to hypersensitivity is still in its infancy. Therefore, the pathway involved in the overexcitation contributing to hypersensitivity remains unclear. Future research could focus on the pathway from the thalamus to S1 as somatosensory stimuli are processed following this trajectory. Given the high prevalence of hypersensitivity in individuals with ASD and the urgency of unravelling the underlying cause of this phenomenon, it is of high importance to study this concept further.

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COLUMN: A THEORY FOR EVERYTHING

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Stephen Hawking has recently posthumously published a final book in which he attempts to provide answers to some of the fundamental questions of existence. Questions such as "Is there a God?", "How did everything begin?" and "Will time travel ever be possible?". In his notes, drafts of answers to all these questions have been found after his passing which, among others, provide a unique insight into one of humankind's most remarkable minds on which the book is based. Additionally, he shows that there is mounting evidence that points toward definitive answers to these questions in physics. He convincingly shows that it is not physically possible for a God to have any impact on the world and provides a conclusive answer for the beginning of time. The only thing that eluded even the great Hawking was the theory that connects general relativity with quantum physics. A theory that is able to integrate both these giants and provide conclusive answers about the nature of the universe is known by physicists as the "Theory of Everything".

There is a growing trend in science to find such theories of everything or, at least a theory that conclusively explains a lot. The latter does not ring well to the ear, however. Humans love to have definitive answers as we tend to think in (binary) classifications. Think of right or wrong, male or female, healthy or sick. There is often little room for nuance or the grey area in between. Even though this is the place where the 'truth' is found in most cases. Because the truth is often not as black-and-white as we like it to be. Take the debate on motivation for example. There are those that argue that intrinsic motivation is best, to do something out of an inherent drive to want to do it. Then there are those that argue that the most realistic form of motivation is extrinsic because it is the most common and mundane form of motivation. However, motivation is not a black-and-white subject. There are many reasons why people act the way they do in certain situations, it is all based on context. Therefore, it is impossible to make claims about which type of motivation is 'the best'. Both are great in their respective contextual situations.

The same goes for communication styles during medical consultations. Currently, there exists a paradigm consisting of three standard consultation models. The paternalistic, the informative and the shared decision-making model. These three models are all practised by competent clinicians who want the best for their patients, but the hard evidence of our time points to the direction that the SDM model is simply "the best". There are dozens of cohort studies, qualitative grounded theory studies, and meta-analyses that all draw this conclusion. Yet, some patients prefer their clinician to make all the decisions, which is the paternalistic model. Then there are patients who have made up their minds about a treatment option and simply want the doctor to prescribe them that. Additionally, there are multiple interpretations of shared decision making and thousands of unique ways of implementing it. I am not saying that this anecdotal evidence disproves the entire theory of shared decision making, because – in most cases – it is the best consultation style a clinician can adopt. I am merely saying that for many things in medicine, and life for that matter, there is no singular truth or a single unifying theory that provides the answers to everything.

Unlike theoretical physics, the domain of the late professor Hawking, medicine is not an exact science. It is mostly comprised of human interaction and everything that is not human interaction is subject to exceptions, discrepancies, and a margin of error. Every medical student knows this, but the curriculum is often not focused on the grey area. Menno de Bree, a Dutch philosopher, wrote in an open letter to medical interns that the Dutch medical curriculum is solely focused on the truth and not on what is moral or interesting. He poses that there should be more attention to these areas in the medical curriculum. I take this a step further by saying that the curriculum should not only focus more on these areas but even more on the truths, plural.

Reaction by Abel Asselbergs

I think "A Theory for Everything" beautifully highlights our desire for definitive answers to our problems. This pursuit of a definitive answer leaves no room for nuance and forces us to think, in what the article refers to as "binary classifications". This idea reminds me of "The Social Dilemma" a 2020 documentary directed by Jeff Orlowski that examines the dangers of social media. Social media platforms use this binary thinking to maximise their profits. They get this opportunity because this black-and-white thinking is the perfect target if you want to polarise two cohorts, for example, anti- versus pro-vaccine groups. Polarising them, by confirming their ideas, leads to hardcore debate and more use of their platforms. As this article shows, binary thinking is not limited to my beforementioned example but found in society as a whole. Physicians are no exception, clinging on to their evidence-based medical protocols – mostly for very good reason – but with next to no regard for any alternative.

It is easy to agree with the article – like I am doing now – and say that this way of thinking cannot be a good trait, it must be 'bad'. However, by saying that, I would be guilty of doing the very thing this article is trying to debunk. So, what is good about it then? Let us not forget that in the medical system we are dealing with a vast number of patients that all deserve the best treatment, but with limited resources. There are a limited number of physicians, limited time, and limited funds. As much as any physician would want to tailor to the specific needs of a patient, for example, by applying the appropriate communications technique, this will only be possible to an extent, it is idealistic. Maybe thinking in a more black-and-white, good-or-bad way allows for a much larger group of patients to receive great medical care as opposed to excellent medical care for a select few. And when resources allow, a physician can always apply a more individualist approach.

Abel Asselbergs
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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Yfke Prins[1]

With over 3,000 publications each year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers – published by researchers from the Radboudumc – will be discussed.

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Mitral annular disjunction as a common result of cardiac imaging

With the technological advances of the last decades, detailed cardiac imaging has become available. Scientists from the Radboud University Medical Centre and the United Kingdom have analysed the presence of mitral annular disjunction on cardiac magnetic imaging (CMR) in participants of the UK Biobank project [1]. Their research was published in JACC Cardiovascular Imaging (Impact factor 16.55). In the UK Biobank project, over 500.000 individuals between 40 and 69 years old in the United Kingdom underwent extensive testing, including genome-wide genotype data. Data from this project was used in this research, which assessed the prevalence of mitral annular disjunction in a study population (predominantly) without a history of cardiac disease. 2,607 participants, who received CMR during the UK Biobank project, were included. The average age of the participants was 61 years. Out of the 2,607 participants, 68 had cardiac arrhythmias, of which six were ventricular arrhythmias. Four participants had survived a cardiac arrest. Other participants had no known risk factors for cardiac disease. In 76% of the participants, a disjunction of the mitral annulus was seen. However, the incidence differed depending upon the location of the disjunction. Inferolateral disjunction was seen in only 5% of the participants. However, disjunction in other locations was found commonly - in 72% of the participants - which raises the question of whether these disjunctions are as pathognomonic as previously thought. The high prevalence of mitral annular disjunction suggests that it is a relatively harmless finding in this age cohort.

Tetraspanin CD37 as a key mediator of fatty acid metabolism in aggressive B-cell lymphoma

CD37-deficiency is associated with a poorer prognosis in diffuse large B-cell lymphoma (DLBCL). This is hypothesised to be due to an alteration in the cell's metabolism, where CD37-deficient DLBCL relies on fatty acid (FA) metabolism, as opposed to glycolysis. Peeters et al. studied the role of CD37 in FA metabolism in DLBCL, which was published in Nature Communications (impact factor 17.7) [2]. Their research suggests that CD37-deficient tumours are indeed dependent upon FA metabolisation, which is mediated through the fatty acid transporter protein 1 (FATP1). This could provide a survival advantage for malignant cells. The switch in metabolism provides energy even under hypoxic conditions, which is often seen in tumours. The switch to FA metabolism was shown using cell lines and animal models. CD37 knock-out (KO) cells showed increased uptake of the fatty acid palmitate, in comparison to DLBCL-positive cells. Furthermore, the CD37 KO cells exhibited an increased mitochondrial respiratory capacity after the administration of palmitate. This effect is thought to occur through an interaction between FATP1 and CD37. FATP1 was prominently expressed in DLBCL cells and colocalized with CD37. Furthermore, it was shown that DLBCL CD37-KO cell lines show a dose-dependent increase in lipid droplets after the administration of palmitate. This seems to suggest that these CD37-deficient cells can form an energy reserve. The FAs, stored in these lipid droplets, could namely be metabolized under hypoxic, nutrient-deficient circumstances, resulting in an additional survival advantage. Therefore, FA metabolism could be a therapeutic target. This was also tested in this study, using a carnitine-palmitoyl-transferase inhibitor. Carnitine-palmitoyl-transferase transports fatty acids into the mitochondria. A dose-dependent decrease in viability and proliferation of CD37KO cells was seen in vitro after the administration of the inhibitor. Thus, this study provides a molecular framework of the intracellular functions of CD37, which could lead to promising therapeutic consequences in the future.

Increased risk of kidney injury for children with a solitary functioning kidney

A solitary functioning kidney (SFK) can be congenital (cSFK) or acquired (aSFK). In both cases, children with SFK are at risk of long-term kidney injury. However, the risk factors are not yet clear. Therefore, Groen in 't Woud et al. conducted the Solitary Functioning Kidney: Aetiology and Prognosis (SOFIA) study [3]. Their study, published in Kidney International (impact factor 19), included 944 children with SFK, diagnosed between 1993 and 2020. The average duration of follow-ups was 12.8 years. The outcome was the incidence of kidney injury, indicated by the urine protein/creatinine ratio, estimated glomerular filtration rate, blood pressure, and the use of antihypertensive or proteinuric medication. At the age of eighteen, 75% of patients with cSFK and 80% of patients with aSFK had at least one indicator of kidney injury. Up to 39% and 37% of the patients with cSFK and aSFK, respectively, developed severe kidney failure. Risk factors for the development of kidney injury were female sex (HR for cSFK/aSFK 1.3, 95% CI 1.1-1.7), severe congenital abnormalities of the kidney and urinary tract (HR 1.3/1.3, 95% CI 1.0-1.7), and high BMI at last follow-up (HR 1.8/1.6, 95% CI 1.0-2.6). Risk factors for severe kidney injury included severe congenital abnormalities of the kidney and urinary tract (HR cSFK/aSFK 1.6/1.5, 95% CI 1.0-2.3), SFK length below p50 (HR 2.0/2.0 95% CI 0.5-8.0), and a high BMI (HR 2.9/2.4, 95% CI 1.2-4.8). Patients with hypodysplasia, i.e. a small or underdeveloped kidney, had a lower risk of severe kidney injury (HR cSFK/aSFK 0.7/0,5, 95% CI 0.3-1.0), as did patients with fetal multicystic dysplastic kidney (HR 0.7/0.7 95% CI 0.4-0.9). This study suggests that children with SFK should receive long-term follow-up, with an emphasis on lifestyle management.

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RAMS

A Word from the Board of RAMS

Dear reader,

Thank you for reading the twenty-fourth edition of RAMS. The past year has been another remarkable one for RAMS, as we continue to play a leading role in the dissemination of knowledge and research in the field of risk assessment, management, and sustainability. Our dedicated team has worked very hard to review and publish a wide range of articles covering the latest advancements and challenges in these areas.

What I have learned so far is that the purpose of scientific articles is to communicate new research findings, theories, and ideas to the scientific community and the general public. Scientific articles serve as a means of disseminating knowledge and advancing the field of study, providing a platform for researchers to share their work, receive feedback, and engage in intellectual discourse.

On behalf of the ninth board of RAMS,

Fatma Shebwana
Vice-chair of the ninth board of RAMS 2022-2023

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RAMS is directed by the general board, which consists of four (bio)medical students. As members of the board, they frequently meet to make sure all activities run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional, or financial subjects, please contact the general board of RAMS via voorzitter.rams@ru.nl.

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