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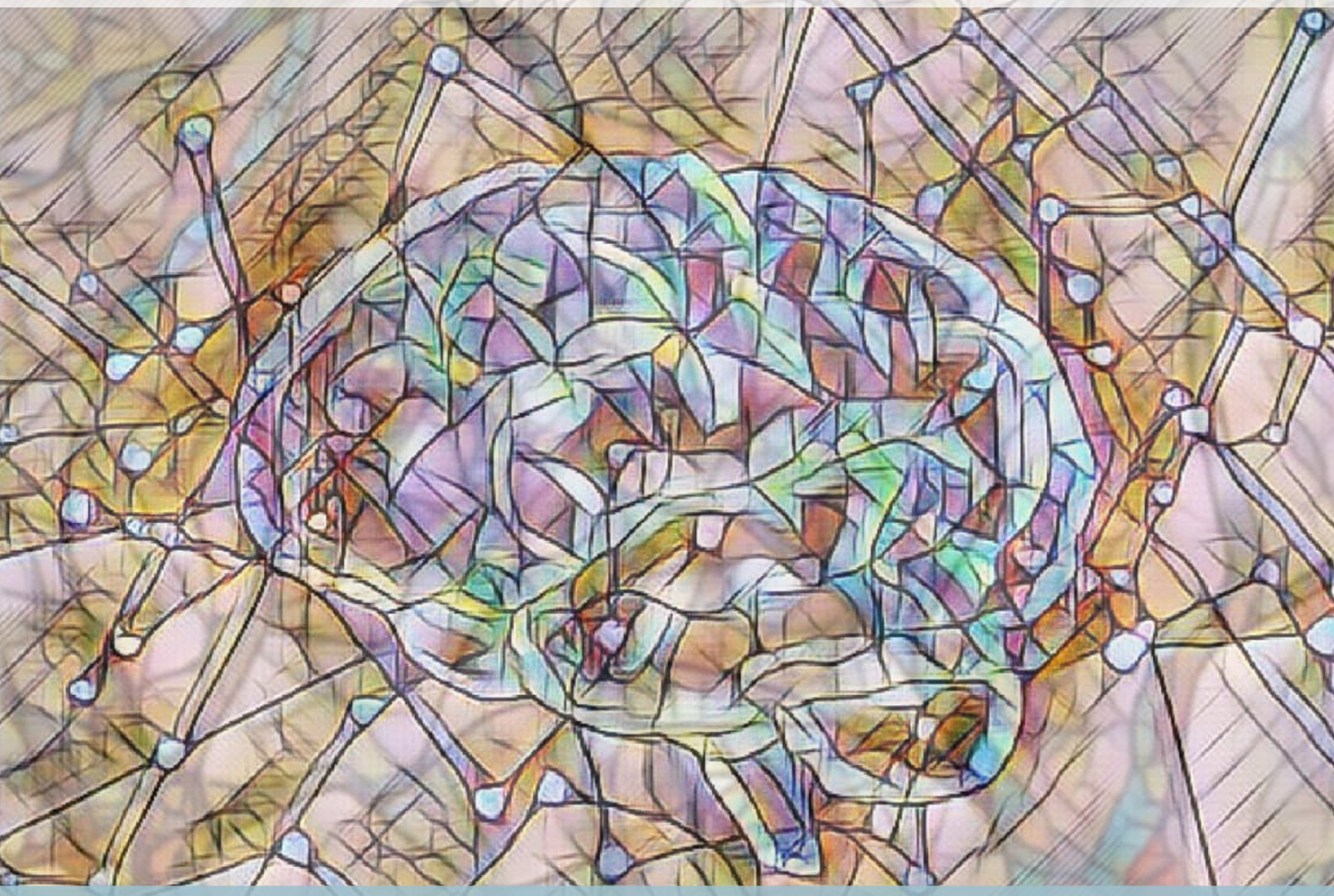

- Wide awake while dreaming: lucid dreaming and its clinical applications
- MDMA-assisted psychotherapy: new hope for treatment-resistant PTSD?
- Interview: science communication in the 21st century
- Similarities and differences between the currently used COVID-19 vaccines

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FROM THE EDITORIAL BOARD

Dear reader,

Thank you for reading this edition, which also marks the last one of this academic year. For those of you who are reading the journal for the first time, welcome!

Ever since I was in elementary school, I have been fascinated by the human body and everything else related to science. During high school, I pretty soon realised that biology and chemistry were my favourite subjects. However, weirdly enough, it took some time to find out that I wanted to include these interests in my future studies and career. At first, I wanted to study medicine and become a medical doctor, but fate (or whatever you want to call it) had other plans for me, and I started studying medical biology. I found a new passion: being engaged in biomedical research to become a scientist!

In our field of study, there are many different subjects to choose from and specialise in, which sometimes can be a struggle when you have a broad interest. Reading about different topics can help solve this problem. This is where RAMS came into play; being involved with the journal as the chair of the editorial board offered me the opportunity to gain more knowledge about different subjects. Working together with students from different disciplines of biomedical science, e.g. medicine, biomedical sciences, and medical biology, gave me the chance to explore biomedical science beyond my area of interest. In the end, it made me realise that all these different subjects and fields of expertise make the world of biomedical science so interesting, fascinating, and challenging at the same time. This broadness of subjects is something we also want to show with the editions of RAMS, to provide students with an opportunity to engage with different disciplines of biomedical science. Therefore, I could not be prouder of this 19th edition. I would like to thank our editors, reviewers, supervisors, chief design, and illustrator for all their time and effort spent on the 19th edition.

In this edition, you can read, amongst others, a comprehensive summary of the currently used COVID-19 vaccines; in the Myth or Science section, you will learn more about the potential of gene therapy for vision loss; and in the Zebras of Medicine section the differences between atopic dermatitis and hyper IgE syndrome are delineated. In addition, have you ever procrastinated studying or finishing an assignment? You are certainly not the only one. There are several psychological and neurological mechanisms explaining this phenomenon. Are you curious? Read further to know more.

We hope that this edition enthuses you (even more) about science. Hopefully, it will inspire you to look beyond your own scientific discipline and dig deeper into subjects that have caught your interest.

Yours faithfully,

Kavita Lips
Chair Editorial Board

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MDMA-ASSISTED PSYCHOTHERAPY: NEW HOPE FOR TREATMENT-RESISTANT PTSD?

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Abstract

Review

Background Following a traumatic event, individuals can develop posttraumatic stress disorder (PTSD). While there are numerous therapy approaches, up to 58 per cent of patients remain treatment-resistant and continue to suffer from PTSD even after several treatment attempts. Thus, the development of novel treatment options is strongly needed to improve the care for this patient group and give them new hope for a life less impacted by PTSD. In the last decades, 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy has been investigated as a potential treatment for treatment-resistant patients.

Objective This review aims to outline the recent developments regarding research on MDMA-assisted psychotherapy to provide the reader with a feel for the potential and feasibility of this new form of treatment. Furthermore, the article aims to briefly delineate the current challenges faced by the field and address widespread doubts regarding the treatment.

Discussion MDMA-assisted psychotherapy consistently showed positive results in treatment-resistant PTSD patients and not only lessened the burden of disease for many but even clinically cured a substantial percentage of partaking patients. Common doubts about the abusive potential of MDMA, as well as dangerous adverse effects, seem to be largely dismissible, and the carried-out studies have given a comfortable framework of how future clinical use could be accomplished. Issues remain regarding the small size of patient cohorts that have so far been included in trials. This shortcoming could introduce a bias in the research results and could result in rare side effects being overlooked.

Conclusion MDMA-assisted psychotherapy is unlikely to be implemented as a first-line treatment for PTSD; nevertheless, it appears to be a promising new approach to treating treatment-resistant PTSD patients and is on track to gain FDA approval for this intent. The results are highly encouraging, and there is little evidence for substantial adverse effects or a high risk of abuse of MDMA in a medical context. Nevertheless, more research, especially studies with larger patient cohorts, is needed to better understand the involved risks and pitfalls of the treatment.

KEYWORDS: Posttraumatic stress disorder, treatment-resistant PTSD, MDMA, 3,4-methylenedioxymethamphetamine;

Posttraumatic stress disorder (PTSD) is a psychiatric condition that develops in about 25-30% of people encountering a single or repeating traumatic event(s) [1]. It is characterised by four clusters of symptoms, namely re-experiencing, negative alterations in cognition/mood, avoidance, and alterations in arousal and reactivity, including hyperarousal and sleep disturbance [2, 3].

Regarding the development of PTSD, the experience of an initial traumatic event X triggers substantial fear [4]. Following a popular model of PTSD development, this event X induces conditioning of the individual to fear a specific occurrence Y that is not directly causative of the fear itself [4]. Hence, a previously unconditioned event Y is associated with the anxiety felt in moment X, and, therefore, whenever that second event (event Y) occurs, the person is subject to the fear again [4]. This further results in avoidance of the trigger Y, which decreases anxiety and, therefore, negatively reinforces the notion that trigger Y is to fear and thus to be avoided [4]. Interestingly, in a rat model of PTSD, PTSD-like symptoms were only achieved when the rats were subject to social instability, additionally to the predatory threat, which is achieved by frequent switching of cage-mates [5]. This finding suggests that social instability is of great importance in PTSD development [5].

Neurobiologically, fear conditioning is controlled by an interplay of several brain structures [6]. The amygdala sends out signals (e.g. the X and Y events) incorporated with other inputs and induces a fear response. These stimuli from the amygdala can be inhibited by the medial prefrontal cortex [4]. In PTSD, the amygdala is hyperactive [7]. This could be, at least partially, rooted in a decrease in the size and activity of the medial prefrontal cortex [8]. Both have been described in twin studies where one twin was exposed to a traumatic event and consecutively did or did not develop PTSD [8]. The resulting fear-induced stress further inhibits the prefrontal cortex, hence, sustaining the fear response via a negative feedback loop [4]. Recently, increased inflammation in the brain in combination with cognitive dysfunction has also been proposed to underlie PTSD. However, more research is needed to fully elucidate its role in PTSD development [9].

The lifetime prevalence of PTSD has been established in numerous studies in the last three decades and shows an interesting pattern based on geographic location. In the United States, several conducted studies found a prevalence of approximately 8%, whereas European studies consistently established a prevalence of 1.3% [10]. Notably, there is a big difference between the sexes, with PTSD being more common among women than men [10]. This variation

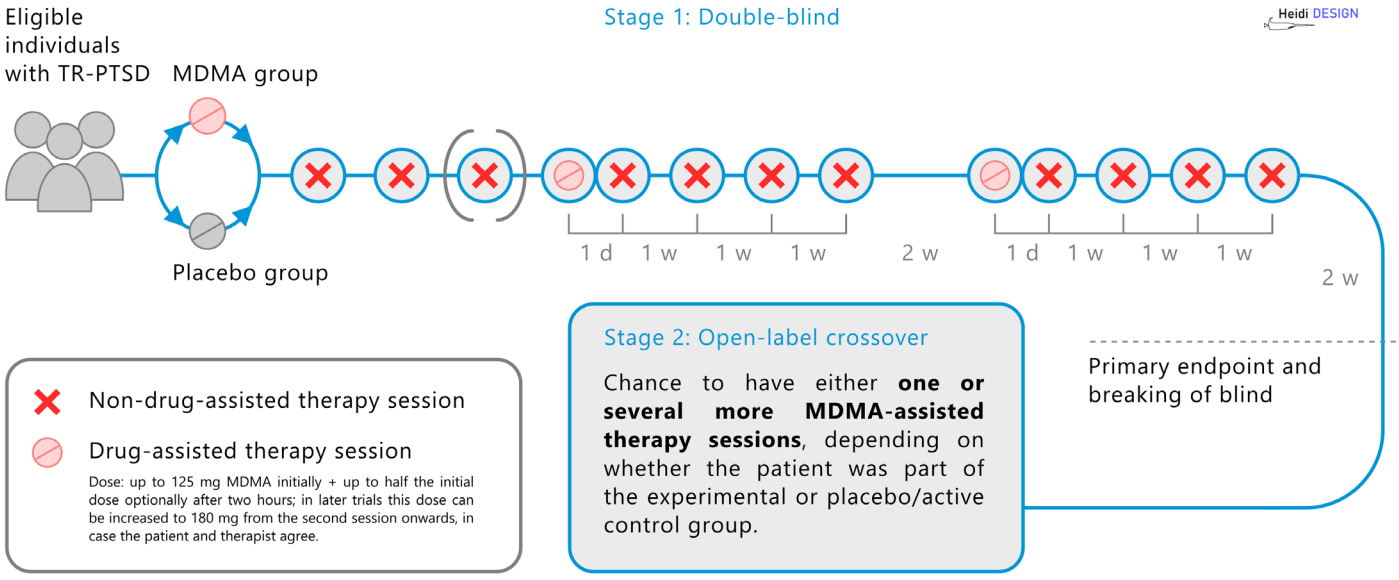

Figure 1: Study design of the clinical trials regarding MDMA-assisted psychotherapy to treat treatment-assisted PTSD. *The figure shows a simplified version of the study design used, with slight variations, in all so far concluded clinical trials. Generally, the study takes place in two stages; the first being the double-blinded phase, while the second one is an open-labelled phase, where placebo group members can switch into the MDMA group. The study subjects are chosen based on various in- and exclusion criteria, the most important being that all have undergone and failed psychotherapy previously, thus, suffering from treatment-resistant PTSD (TR-PTSD). The eligible patients are then classified randomly in a control group, receiving the placebo, and in one or more MDMA groups, receiving MDMA at concentrations between 30 and 125 mg. The substance administration as well as all therapy sessions and the scoring at the primary endpoint take place under double-blinding conditions. All study participants receive two to three preparational therapy sessions before taking part in one of two substance-assisted therapy sessions of about six to eight hours. The substance-assisted therapy sessions are directly followed by an overnight stay in the hospital, a non-drug-assisted therapy session the following day, and daily phone contact with the therapist for the next week, as well as three weekly non-drug assisted therapy sessions. At the end of stage one, the patients are scored according to the Clinician-Administered PTSD Scale to determine the extent of their dysfunctionality due to their PTSD. Next, the double-blinding is broken, and patients of the control group (and in the case of the phase II trials, patients receiving lower doses of MDMA) are offered the possibility to switch to the treatment group and receive further MDMA-assisted therapy sessions. The details on this phase have been omitted from the figure due to clarity and can be found in the individual descriptions in the literature. Furthermore, the studies include an observational period of about two to twelve months.*

is consistent with other stress disorders, although little is known about the underlying reason [10]. The possibility that PTSD only develops delayed following a traumatic event further complicates the identification and treatment of the patients; however, there is evidence that patients profit from treatment, even when this treatment is only given late into their condition [1, 11].

PTSD can have drastic consequences for the quality of life of a patient and severely disrupt their lives; hence, successful treatment is crucial to lessen the burden [4]. Moreover, PTSD commonly appears alongside other psychiatric disorders, such as major depression and anxiety disorders, or physical comorbidities like cardiovascular disorders [4]. An association between PTSD and cancers and PTSD and gastrointestinal diseases has been proposed, albeit the research results remain inconclusive [4]. These comorbidities further underscore the importance of successful treatment of the patient.

Treatment options for PTSD

First-line treatment of PTSD conventionally consists of different forms of psychotherapy, all of which focus on confronting the trauma while in a safe space and processing the traumatic memories and accompanying feelings [1, 4]. More recently, also drug treatments alone (e.g. antidepressants like serotonin-reuptake inhibitors) or in combination with psychotherapy (e.g. antipsychotics) were proposed for PTSD, although for now, they remain second-line treatment options compared to psychotherapy alone [1].

Unfortunately, up to 58% of patients show PTSD symptoms even after first-line treatment, leaving a substantial part of patients without improvement [12]. A new treatment approach proposed for these treatment-resistant PTSD cases is repetitive transcranial magnetic stimulation in combination with psychotherapy [13]. In this non-invasive technique, repetitively changing electromagnetic fields are transmitted to the scalp of the patient [13]. If combined with psychotherapy, repetitive transcranial magnetic stimulation has been shown to have antidepressant effects and improve PTSD symptoms [13]. However, study designs varied considerably between the studies included in the analysis of Namgung *et al.*, and, thus, more research in this field is duly needed before the treatment can be made accessible to the majority of patients [13].

Another option of treating treatment-resistant PTSD is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy [14]. This review aims to give an overview of the current state of the field and outline the progress made regarding this new treatment variation.

MDMA-supplemented psychotherapy in PTSD

MDMA primarily acts to raise levels of serotonin, dopamine, and norepinephrine in the synaptic cleft between neurons by promoting their release and inhibiting their reuptake [14]. Psychological effects include enhancement in mood and well-being, as well as thought disorder and moderate depersonalisation [15]. These effects, in combination with a decrease in anxiety and an increase in

interpersonal closeness, could, potentially, substantially aid patients during psychotherapy targeting anxiety disorders like PTSD [14].

The worldwide first pilot study of MDMA-assisted psychotherapy got prematurely terminated in 2002 due to political opposition [16]. However, in 2010, the first clinical trial was concluded and showed promising results [16, 17]. The study was designed to be randomised and double-blinded and included 20 treatment-resistant PTSD patients (Figure 1) [17]. Twelve individuals received 125 mg MDMA (plus an optional dose of 62.5 mg after approximately two hours) for two therapy sessions of eight hours each. The remaining eight patients forming the smaller control group received a placebo [17]. Each individual substance-assisted therapy session was followed up with an overnight stay at a hospital as well as three regular therapy sessions, and the substance-assisted therapy sessions were one month apart [17]. The response rate was defined as >30% reduction of the individual "Clinician-Administered PTSD Scale" score, which is the gold standard of PTSD classification [17].

The results were encouraging, with MDMA-assisted therapy showing a response rate of 83% (10/12 patients) versus 25% (2/10 patients) in the control group [17]. This means that ten patients in the MDMA group no longer met the criteria for a PTSD diagnosis, whereas this was only the case for two patients in the placebo group [17]. Following the study's conclusion, control individuals were offered the possibility to crossover into the treatment group [17]. This group then showed a response rate of 100% [17]. A follow-up of 16 of the study participants concluded that this improvement was sustained for a median of 45 months, and the mean "Clinician-Administered PTSD Scale" score at the study exit was not significantly different from the "Clinician-Administered PTSD Scale" score at the end of the long-term evaluation [18].

A later study by Oehen and colleagues from New Zealand in 2013 failed at first glance to replicate these results and instead showed no improvement of MDMA-supplemented psychotherapy compared to placebo-supplemented psychotherapy [19]. However, a later re-analysis of the data pointed out that the previous interpretations were probably overly stringent as "the conclusion is based on improper reliance on statistical analyses inappropriately used on such a small sample" [20]. Thus, the results were, in fact, supporting the findings of Mithoefer *et al.* rather than contrasting them [20]. Recently, several phase II trials have been conducted, all of which had very similar study designs like the one concluded by Mithoefer *et al.* in 2010 (Figure 1) [21-23]. Not only was the severity of PTSD symptoms in patients reduced following MDMA-supplemented psychotherapy in these studies, but also, approximately twice as many patients of the MDMA group did no longer meet the criteria for PTSD compared to the control group. These results further strengthened the case of MDMA-supplemented psychotherapy as a treatment for treatment-resistant PTSD [22, 23].

Together, these data have paved the way for phase III trials in the United States, Canada, and Israel, one of which has already been concluded [14, 23]. While the experimental data is still under review, data on adverse side effects have been made public in the MDMA Investigators Brochure of the Multidisciplinary Association for Psychedelic Studies (MAPS) [14]. MAPS strongly supports research into MDMA-assisted psychotherapy, as well as other psychedelics-related studies [14]. Most commonly reported side effects included muscle tightness, decreased appetite, and nausea, all of which resolved seven days after MDMA administration at the latest [14]. Prevalence of suicidal thoughts, suicidal behaviour, or substance abuse was equal to or, in the case of suicidal ideation, even reduced compared to the placebo group [14]. Altogether, research remains on track, and, following completion of the second phase III trial, MAPS plans to seek approval of the FDA for MDMA as a supplement to psychotherapy in treatment-resistant PTSD [14].

Challenges, indication, and use in other disorders

Despite the promising results gathered so far and the good pace at which research on MDMA-assisted therapy progresses, several challenges remain. One of the most prominent doubts refers to the abuse potential of MDMA, seeing as it is, for now, classified as an illegal substance. Several animal experiments explored the addictive potential of self-administration of MDMA. These studies outlined that MDMA does have the potential for abuse, although this seems to be less than for other illegal substances, such as cocaine or heroin [14]. Data on drug abuse by patients following their participation in MDMA trials highlighted only a small abuse potential, as not a single participant thought of abusing any illegal substance for at least 17 months post-trial [18]. Similar results were gathered from later phase II trials and the previously finished phase III trial [14, 22, 23]. Here, three subjects of the MDMA group acknowledged using cannabis post-trial. However, it has to be highlighted that the trial purposefully included treatment-resistant PTSD patients that may or may not have a mild-moderate substance abuse problem at the beginning [14]. Thus, cannabis use does not necessarily derive from the administration of MDMA during the trial [14]. Nevertheless, despite the apparent relatively low abuse potential, the addictive nature of MDMA will have to be kept in mind during treatment. Hence, the administration needs to be tightly regulated, and the patients need to be closely monitored. The so-far carried-out studies provide the clinicians with a well-thought-out framework of what future clinical implementation of MDMA-assisted psychotherapy could look like.

Another remaining challenge is that the outlined data stem exclusively from studies with small participant numbers. This could potentially introduce a bias and cause rare side effects not to become apparent. Moreover, larger cohorts allow for more diversity among participants, hence, improving the validity of the data. Thus, trials with higher patient numbers are strongly needed to guarantee the patients' safety and well-being.

Notably, the risks, extensive necessary surveillance, and related costs make the treatment unlikely to be implemented as a first-line treatment [24]. Instead, the treatment would be offered as a new chance for patients who fail to respond to other forms of treatment or do not wish to undergo pharmacological treatments using antidepressants. Apart from PTSD, the use of MDMA-assisted psychotherapy has also been discussed for other disorders [25, 26]. MAPS has so far conducted trials for several anxiety disorders, and a new one is planned for a combinational cohort of patients with anorexia nervosa and binge eating [14].

Conclusion

In the last two decades, research on MDMA-assisted psychotherapy has consistently gathered highly promising results concerning treatment-resistant PTSD patients and seems on its way into clinical practice. Importantly, MDMA-assisted psychotherapy is not aiming at replacing other first-line therapies for PTSD; rather, it would come into play where other treatments failed. Data on the toxicity and adverse effects of MDMA itself show the substance to be reasonably safe. However, due to its inherent addictive potential, strict regulations will be necessary to keep risks of abuse as low as possible. As MDMA is still widely regarded as an illegal substance,

research on it remains challenging, especially in the aspect of larger trials. However, precisely these studies will be necessary to improve the understanding of the potential risks as well as the benefits of MDMA in the context of assisting psychotherapy. The coming years could very well bring a fundamental change of mentality towards MDMA and its place as an assisting substance to psychotherapy, not only in PTSD therapy but also in the treatments of other anxiety disorders.

Acknowledgement

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References

1. National Institute for Health and Care Excellence. Post-traumatic stress disorder (NICE Guideline 116). (2018).
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed), (American Psychiatric Association, Arlington, 2013).
3. Ross, R.J., *et al.* Sleep disturbance as the hallmark of posttraumatic stress disorder. *The American Journal of Psychiatry* **146**, 697-707 (1989).
4. Ellis, J. & Zaretsky, A. Assessment and Management of Posttraumatic Stress Disorder. *CONTINUUM (MINNEAP MINN)* **24**, 873–892 (2018).
5. Zoladz PR, Diamond DM. Predator-based psychosocial stress animal model of PTSD: Preclinical assessment of traumatic stress at cognitive, hormonal, pharmacological, cardiovascular and epigenetic levels of analysis. *Exp Neurol* **284**, 211-219 (2016).
6. Shin, L.M., *et al.* Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci* **1071**, 67-79 (2006).
7. Koenigs, M. & Grafman, J. Posttraumatic Stress Disorder: The Role of Medial Prefrontal Cortex and Amygdala. *The Neuroscientist* **15**, 540-548 (2009).
8. Dahlgren, M.K., *et al.* Diminished medial prefrontal cortex activation during the recollection of stressful events is an acquired characteristic of PTSD. *Psychol Med* **48**, 1128-1138 (2018).
9. Quinones, M.M., *et al.* Dysregulation of inflammation, neurobiology, and cognitive function in PTSD: an integrative review. *Cogn Affect Behav Neurosci* **20**, 455-480 (2020).
10. Gradus, J.L. Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. *Clin Epidemiol* **9**, 251-260 (2017).
11. Bisson, J.I., *et al.* Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev*, CD003388 (2013).
12. Morgan, L. MDMA-assisted psychotherapy for people diagnosed with treatment-resistant PTSD: what it is and what it isn't. *Ann Gen Psychiatry* **19**, 33 (2020).
13. Namgung, E., *et al.* Repetitive transcranial magnetic stimulation in trauma-related conditions. *Neuropsychiatr Dis Treat* **15**, 701-712 (2019).
14. Multidisciplinary Association for Psychedelic Studies (Maps). MDMA Investigator's Brochure and Development Safety Update Report (13th ed). (2021).
15. Vollenweider, F.X., *et al.* Psychological and Cardiovascular Effects and Short-Term Sequelae of MDMA ("Ecstasy") in MDMA-Naïve Healthy Volunteers. *Neuropsychopharmacology* **19**, 241-251 (1998).
16. Bouso, J.C., *et al.* MDMA-Assisted Psychotherapy Using Low Doses in a Small Sample of Women with Chronic Posttraumatic Stress Disorder. *Journal of Psychoactive Drugs* **40**, 225-236 (2008).
17. Mithoefer, M.C., *et al.* The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol* **25**, 439-452 (2011).
18. Mithoefer, M.C., *et al.* Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol* **27**, 28-39 (2013).
19. Oehen, P., *et al.* A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *J Psychopharmacol* **27**, 40-52 (2013).
20. Chabrol, H. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *J Psychopharmacol* **27**, 865-866 (2013).
21. Feduccia, A.A., *et al.* Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. *Front Psychiatry* **10**, 650 (2019).
22. Mithoefer, M.C., *et al.* 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry* **5**, 486-497 (2018).
23. Mithoefer, M.C., *et al.* MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl)* **236**, 2735-2745 (2019).
24. Chi, T. & Gold, J.A. A review of emerging therapeutic potential of psychedelic drugs in the treatment of psychiatric illnesses. *J Neurol Sci* **411**, 116715 (2020).
25. Danforth, A.L., *et al.* Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology (Berl)* **235**, 3137-3148 (2018).
26. Wolfson, P.E., *et al.* MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Sci Rep* **10**, 20442 (2020).

MYTH OR SCIENCE? KEEP YOUR EYE PEELED
GENETIC THERAPIES FOR INHERITED RETINAL DISORDERS

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Critical appraisal

"There is nothing we can do"; Creed Pettit and his family had heard this phrase over and over again [1]. Being born with an inherited form of retinal degeneration, Creed spent all his youth being fully dependent on flashlights and lamps to see properly. Unfortunately, his condition would only get worse, and Creed would eventually completely lose his sight as he got older. Yet, there was light at the end of the tunnel. At the age of nine, Creed was treated with Luxturna®, the first FDA-approved gene therapy drug for an inherited retinal disease, becoming the youngest person in the United States to receive this therapy [2, 3]. A few days after his treatment, Creed's vision had already improved. A month later, Creed was not in need of his flashlights anymore and could slowly start living a normal life. It was a miracle! Following Luxturna®, new versions of the technology have been developed over the years. Currently, the field is expanding rapidly, with hundreds of clinical trials investigating the efficacy of such gene therapies in hereditary retinal diseases. However, with scepticism around the feasibility, long-term efficacy, and costs of genetic therapies, their use in the clinic is still controversial. Can genetic therapies be used to cure inherited retinal disorders, and will they become a standard treatment option for all cases of such eye disorders?

Missing one of your senses might sound unbearable for most, but for blind people, it is reality. In 2017, it was estimated that, globally, about 36 million people suffer from blindness [4, 5]. Blindness can be the result of refractive errors, age, and trauma, or it can be inherited through genetic mutations [6, 7]. More than 190 genes are involved in inherited retinal disorders, and besides this high genetic variability, substantial clinical heterogeneity is also observed. For example, retinitis pigmentosa, which accounts for most cases of inherited retinal degeneration, can be caused by at least 50 genes [6, 7]. Examples of these are the *retinal pigment epithelium-specific 65* (*RPE65*) and *rhodopsin* (*RHO*), both expressed in the retina of the eye [6, 7]. Retinal degenerative diseases usually present as an impairment of night or colour vision and progress with loss of peripheral and central vision. Conventional strategies to manage vision impairment are limited to refractive correction (e.g. use of eyeglasses) or surgery [8, 9]. However, such therapies are not effective for inherited or complex forms of blindness [8]. Unfortunately, no pharmacological treatments are available either. Over the past years, however, considerable progress in molecular technologies has expanded the toolbox of scientists. With such increasing knowledge, will we be able to fully cure inherited retinal diseases?

How does it work?

Genetic mutations and consequent abnormalities in protein expression or function form the basis of hereditary disorders. Such genomic abnormalities can disrupt entire chromosomes or be of a smaller scale, affecting one or few genes within one chromosome [10]. Genetic therapies focus on the latter genomic alterations to treat a hereditary disease. Here, genetic material is introduced into specific cells of a patient to correct for the underlying genetic mutation (Figure 1) [6, 11]. The transferred genetic material can repress, enhance, or alter the expression of disease-causing genes. For instance, a functional copy of the gene can be inserted into the patient's cells to correct for the malfunctioning gene and restore the gene's normal protein activity (gene supplementation) [11]. Alternatively, genetic constructs can be used to repair the disease-causing mutation or inactivate the non-functional copy of a gene of interest. In the last two strategies, gene editing can be carried out in different ways, including CRISPR-Cas9 and exon skipping [12].

After their "manufacturing", these DNA constructs need to be delivered to the patient's cells. However, naked DNA cannot be introduced directly into your cells [13]. Hence, to do so, they are delivered in special carriers, known as vectors (Figure 1) [13]. For this purpose, viruses modified to carry the genetic material of interest can be used as vectors. Adeno(-associated)viruses, lentiviruses, and retroviruses are commonly used. Non-viral delivery methods exist as well; however, they have a lower gene transfer efficiency than viral vectors [11]. In the case of retinal diseases, the DNA/vector constructs can be directly injected into the eye (Figure 1). Common areas of injection include the vitreous cavity located behind the lens (intravitreal injection) and the subretinal space beneath the retina of the eye (subretinal injection) (Figure 1) [6].

Why the eye?

The eye is a particularly suitable organ for genetic therapies for multiple reasons. Firstly, eyes are immune-privileged sites, meaning that immune responses are suppressed here [14]. This property of the eyes is favourable for genetic therapy, as no strong immune responses against the viral delivery vectors can be mounted [15]. Besides, since the eyes are positioned in tight cavities separated from the rest of the body, the chance of systemic viral contamination is low [15]. Furthermore, retinal cells do not regenerate or spontaneously mutate, which is suitable for the long-term expression and functioning of the DNA constructs delivered through genetic therapies [16]. Finally, due to their location, eyes are easily accessible by injections, which makes them highly suitable for such therapies [15].

The promise of genetic therapies

Following the success and overall safety of gene therapies in rodent and larger animal models, such therapies have been tested in multiple clinical trials for hereditary retinal diseases [17, 18]. The first gene therapy for inherited blindness approved in the clinic, Luxturna®, contains the functional (wild-type) copy of *RPE65*, which encodes an enzyme involved in vision [2]. Mutations in *RPE65* are reported in multiple retinal degenerative disorders, such as Leber congenital amaurosis type 2 (LCA2), where dysfunctional *RPE65* disrupts the conversion of light into electrical signals that stimulate vision [2, 3]. Subretinal injections of Luxturna® in patients with *RPE65*-related retinal dystrophy improved their visual and navigational abilities. Besides, patients treated with the *RPE65*-based gene therapy

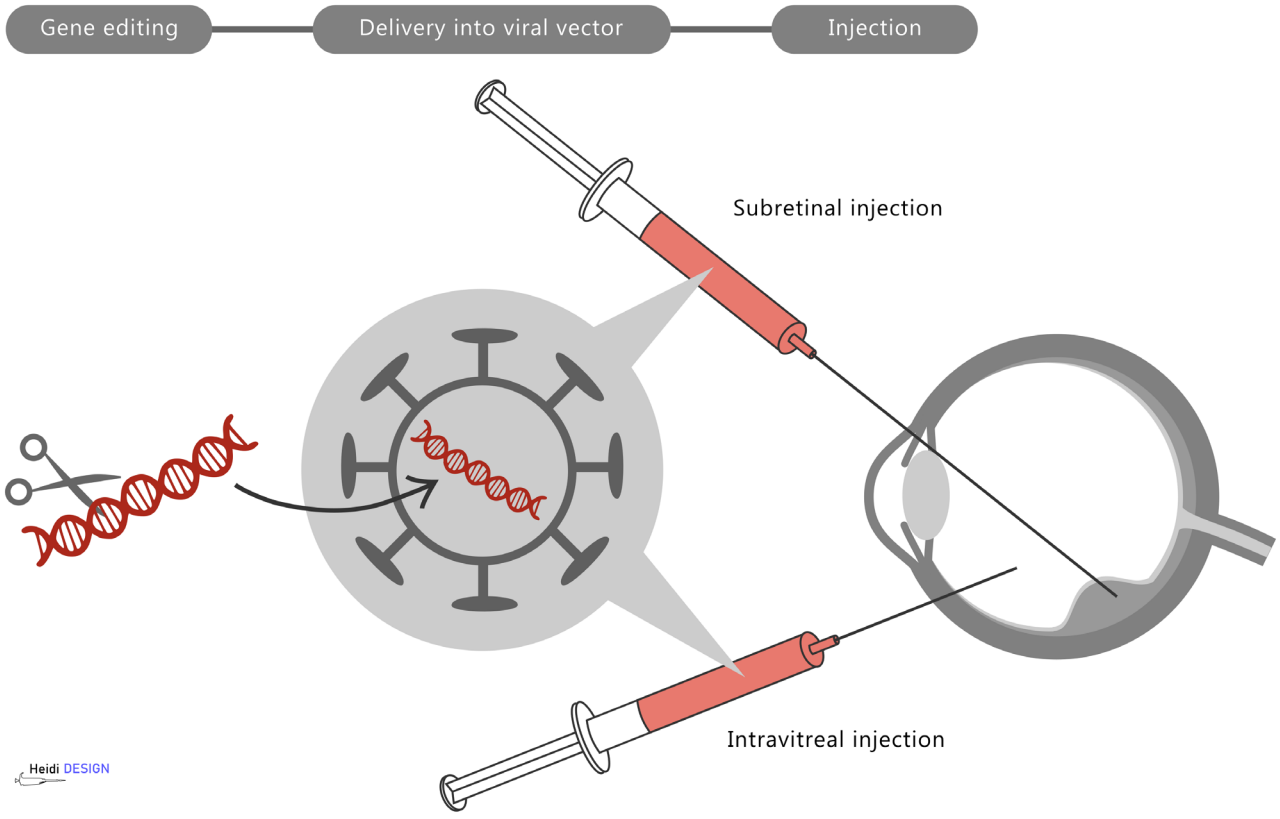

Figure 1: *The general approach of genetic therapies. After manufacturing the DNA constructs of interest (gene editing), they are packaged into viral vectors and administered to the eye of the patient by subretinal or intravital injections.*

also showed changes in the visual cortex, suggesting that the brain is responsive to the gene therapy as well [19].

Following Luxturna®, more genetic therapy technologies have been tested for multiple forms of hereditary vision loss [20]. Supplementation of *MERTK (MER Proto-Oncogene, Tyrosine Kinase)* and *CHM (Choroideremia)* in patients suffering from inherited retinal diseases has shown encouraging results in early phase clinical trials [20]. In 2020, 43 clinical trials using genetic therapy against inherited retinal disorders had been reported, with promising candidates among them [20]. Interestingly, following gene therapy, improvement of vision in the non-treated eye has been reported as well. In a phase III trial, intravitreal injection of the functional copy of the disease-causing gene in one eye of the patient improved vision in both eyes [21]. Even though more research is needed, such improvement is thought to be the result of the movement of the injected genetic construct from one eye to the other [21]. Moreover, whether this is an event specific to this subset of inherited retinal disorder is also not known.

Besides gene supplementation, other genetic therapy methods have been tested in patients [22]. A promising example is the use of antisense oligonucleotides (AONs) [22]. AONs are short synthetic DNA or RNA sequences that are complementary to and can bind to RNA to alter protein expression [22]. Through AONs, errors during pre-mRNA splicing can be repaired. In a recent clinical trial, Sepofarsen®, an AON targeting the *CEP290* mRNA, has been tested for the treatment of LCA [23]. Intravitreal injections of Sepofarsen® showed a safe profile and improved the ability of LCA patients to discern visual details [23].

More advanced versions of the technology are being developed and tested in preclinical models with the promise to be introduced in the clinics [24]. Among them is the use of a modified CRISPR-Cas9 version, dead Cas9 (dCas9) [24]. With dCas9, scientists can activate the expression of proteins functionally equivalent with the disease-causing protein [24]. A recent study used this technology in a mouse model of retinitis pigmentosa to stimulate the expression of a gene that can functionally replace *RHO*. Subretinal injections of viral vectors containing this dCas9 construct resulted in improved retinal activity, which was stable for at least one year after the injection [24].

Is genetic therapy suitable for all patients?

Even though genetic therapies are promising, they might not be the solution for all patients [12]. Inherited retinal degeneration can be the result of a large variety of mutations in multiple genes [12]. To date, many disease-causing genes have been identified but, due to limitations in the technologies used to identify causal genes, many also remain to be discovered. As a consequence, patients with an unknown cause of genetic blindness cannot benefit from genetic treatment. Furthermore, with genetic therapies, only one gene can be targeted at a time [12]. When considering the genetic heterogeneity of retinal disorders, the number of patients that can benefit from a single genetic therapy correction is low as only a few patients would be eligible for each one. Besides, patients suffering from retinal degenerative disorders with more complex genetics will be more difficult to treat with genetic treatment. The disease stage should be considered as well; in advanced stages, extensive retinal degeneration limits the efficacy of viral vector delivery. Thus, in such cases, intervening with a genetic therapy would be ineffective. Finally, the high costs associated with the development and distribution of

genetic therapies can be limiting for some patients and the public healthcare system as a whole.

Conclusion

A decade ago, no cure for severe forms of visual impairment existed. Genetic therapies not only revolutionised medicine but also promised what no other therapy could, a possible cure for previously incurable diseases such as genetic blindness. Currently, new and improved versions of genetic therapies are being developed and tested for their efficacy in treating different types of hereditary retinal diseases. Even though such therapies hold great promise, several steps need to be taken before they become the standard of care for all patients with genetic visual impairment. Still, the incredible story of Creed Pettit gives hope to many patients around the world and inspires to perform more research into genetic therapies**.**

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References

1. American Academy of Ophthalmology. Blind boy sees after gene therapy [Internet]. [updated 14-05-2018; cited 25-04-2021]. Available from: https://www.aao.org/eye-health/patient-stories-detail/creed-gene-therapy.
2. Russell, S., *et al.* Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *The Lancet* **390**, 849-860 (2017).
3. Smalley, E. First AAV gene therapy poised for landmark approval. Nature Publishing Group (2017).
4. Bourne, R.R., *et al.* Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. The *Lancet Global Health* **5**, e888-e897 (2017).
5. World Health Organization (WHO). Blindness and vision impairment [Internet]. [updated 26-02-2021; cited 31-03-2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment.
6. Dalkara, D., *et al.* Let there be light: gene and cell therapy for blindness. *Human gene therapy* **27**, 134-147 (2016).
7. Daiger, S., *et al*. Genes and mutations causing retinitis pigmentosa. *Clinical genetics* **84**, 132-141 (2013).
8. Yorston, D. Retinal diseases and vision 2020. *Community Eye Health* **16**, 19-20 (2003).
9. Dandona, R. & Dandona, L. Refractive error blindness. *Bulletin of the World Health Organization* **79**, 237-243 (2001).
10. National Human Genome Research Institute (NHGRI). Genetic disorders [Internet]. [updated 18-05-2018; cited 31-03-2021]. Available from: https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders
11. Mammen, B., *et al*. Principles of gene therapy. *Indian Journal of Dental Research* **18**, 196 (2007).
12. Lee, J.H., *et al*. Gene therapy for visual loss: opportunities and concerns. *Progress in retinal and eye research* **68**, 31-53 (2019).
13. Van Tendeloo, V., *et al*. Gene therapy: principles and applications to hematopoietic cells. *Leukemia* **15**, 523-544 (2001).
14. Forrester, J.V. & Xu, H. Good news–bad news: the Yin and Yang of immune privilege in the eye. *Frontiers in immunology* **3**, 338 (2012).
15. Samiy, N. Gene therapy for retinal diseases. *Journal of ophthalmic & vision research* **9**, 506 (2014).
16. Martin, J.F. & Poché, R.A. Awakening the regenerative potential of the mammalian retina. *Development* **146** (2019).
17. Colella, P. & Auricchio, A. AAV-mediated gene supply for treatment of degenerative and neovascular retinal diseases. *Current gene therapy* **10**, 371-380 (2010).
18. Acland, G.M., *et al.* Gene therapy restores vision in a canine model of childhood blindness. *Nature genetics* **28**, 92-95 (2001).
19. Ashtari, M., *et al*. The human visual cortex responds to gene therapy–mediated recovery of retinal function. *The Journal of clinical investigation* **121**, 2160-2168 (2011).
20. Fuller-Carter, P.I., *et al*. Focused Update on AAV-Based Gene Therapy Clinical Trials for Inherited Retinal Degeneration. *BioDrugs*, 1-19 (2020).
21. Yu-Wai-Man, P., *et al*. Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. *Science translational medicine* **12** (2020).
22. Rinaldi, C. & Wood, M.J. Antisense oligonucleotides: the next frontier for treatment of neurological disorders. *Nature Reviews Neurology* **14**, 9 (2018).
23. Russell, S.R., *et al*. Intravitreal Sepofarsen for Leber Congenital Amaurosis Type 10 (LCA10). *The Lancet* **34**, 763-781 (2020).
24. Böhm, S., *et al*. A gene therapy for inherited blindness using dCas9-VPR–mediated transcriptional activation. *Science advances* **6**, eaba5614 (2020).

ACADEMIC PROCRASTINATION
THE UNDERLYING PSYCHOLOGICAL AND NEUROLOGICAL FACTORS

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Abstract

Summary

Academic procrastination is observed in 50-75% of students and is associated with several adverse effects on personal well-being and academic performance. Traditionally, academic procrastination is defined as voluntarily and irrationally delaying studying-related tasks. However, many discrepancies appeared in both psychological as well as in neurological research on procrastination. These inconsistencies resulted in a reinvestigation of the traditional outlook on procrastination, which led to the distinction between passive and active procrastination. Whereas passive procrastination is mainly associated with low self-control and high impulsivity, active academic procrastination is associated with extraversion and emotional stability. In other words, in active procrastination, the choice to delay tasks is made on purpose and not primarily to delay unpleasant tasks. The introduction of these two types of procrastination enhanced further research on this matter, which made it possible to further unravel the different neurological pathways involved in procrastination, as well as develop theoretical frameworks that can explain procrastination. The aim of this article is to elaborate on the underlying psychological and neurological factors in academic procrastination, describing both the several traits, cognitive aspects, and task characteristics that form the four theoretical frameworks that can explain academic procrastination, as well as elaborating on the subregions of the brain that are involved.

KEY WORDS: Task aversiveness, temporal decision theory, limbic system, prefrontal cortex, anterior cingulate cortex

Procrastination is often defined as the act of voluntarily delaying certain tasks and/or activities despite acknowledging that the delay will not result in more beneficial outcomes [1]. One form of procrastination is academic procrastination, which is a well-known phenomenon and refers to procrastination of learning- and studying-related actions [2]. In a study among undergraduates in China from 2018 (n = 1184), academic procrastination was reported in 74% of students [3]. A prevalence of 52% was found in another study from 2009 among Turkish students (n = 784) [4].

Academic procrastination can result in reduced personal well-being, and it can have negative effects within the academic domain [2]. An interview study among university students identified stress, illness, and exhaustion as health-related adverse effects of academic procrastination [5]. In addition, feelings of shame, anger, anxiety, a negative self-image, and social problems were frequently reported [5]. Another interview study among university counsellors produced similar findings [6]. Moreover, academic procrastination was found to be associated with lower grades, in particular coursework grades [7, 8].

Nevertheless, academic procrastination does not only have negative consequences [9, 10]. Chu *et al.* were the first to distinguish active from passive procrastination [9]. Passive procrastinators procrastinate to avoid tasks, which results in failure to complete the task in time, whereas active procrastinators decide to procrastinate intentionally, giving preference to working under time pressure [9]. Positive consequences of active procrastination include time efficiency, increased academic performance, and the perception of being in control of the situation [9, 10].

The causes and risk factors of academic procrastination have been studied extensively [1, 2, 11]. Several personality traits and task-level characteristics have been identified that contribute to procrastination from a more psychological view [1, 2, 11]. Consequently, various theoretical frameworks have been developed [1, 2, 11]. Building on these psychological theories, cognitive neuroscientists have studied the brain mechanisms underlying academic procrastination. From this perspective, the interplay between the limbic system and the prefrontal cortex are of particular interest. This article aims to elaborate on the factors underlying academic procrastination from both a psychological and neurological perspective.

Psychological perspective on procrastination

Many studies have reported psychological mechanisms underlying academic procrastination [1, 2, 11]. From this literature, the following general topics can be distinguished as psychological factors in academic procrastination: personality, cognitive ability, and task characteristics. Various theoretical frameworks on procrastination have been developed based on these psychological factors.

Personality

With regard to personality, two models have been used in research: the five-factor model of personality and the temperament and character model [12-15]. The five-factor model is most commonly used and distinguishes the following traits: agreeableness (e.g. kindness, generosity, helpfulness), conscientiousness (e.g. self-discipline, striving for achievement), extraversion (e.g. enthusiasm, sociability, high-energy), neuroticism (e.g. emotional instability), and openness (e.g. imaginativeness, curiosity) [12, 13].

Having low conscientiousness is a well-established predictor of academic procrastination [16-19]. Self-discipline, i.e. resistance to temptations or control over one's desires and emotions, is a facet of conscientiousness [12, 13]. Individuals with little self-discipline tend to prefer short-term satisfaction over long-term benefits, and,

thus, they are more vulnerable to procrastination [11]. Impulsivity, a facet of neuroticism, is the tendency to display behaviour with little or no forethought and is often aimed at satisfying short-term needs [11-13]. While some studies indicate that neuroticism predicts procrastination, others show weaker or no association [16-21]. Regarding the other three traits of the five-factor model, i.e. agreeableness, extraversion, and openness, results are even more inconsistent.

However, this inconsistency is partly solved by distinguishing between passive and active academic procrastination [9, 10]. Emotional stability (the opposite of neuroticism) and extraversion are predictors of active academic procrastination, in which the decision to procrastinate is made deliberately and with the intention to fulfil tasks in a time-efficient manner [10, 22, 23]. As an illustration, extroverts generally enjoy participating in many social activities and having busy schedules [22, 23]. A full schedule requires planning, which explains why extraverts are more likely to procrastinate actively [22, 23]. Altogether, passive and active procrastinators differ in personality, and, thus, they have different motives for procrastination.

Another way to study procrastination in light of personality is the temperament and character model [14, 15]. Temperament manifests in early development, while a character is developed later during life [14, 15]. Character is affected by one's temperament and socio-environmental factors [14, 15]. A dependable temperament profile is characterised by being highly affected by rewards, persistent but not afraid to take risks, and having low levels of novelty seeking [24, 25]. A well-developed character is defined by high levels of self-directedness (i.e. self-acceptance and personal goal development), cooperation, and self-transcendence (i.e. feeling part of the bigger picture) [24, 25]. The dependable temperament- and well-developed character profiles have previously been associated with health and happiness [24]. Both profiles are more often established in active than in passive procrastinators [25]. As an example, active procrastinators display lower levels of novelty seeking, meaning that their decisions rely less on impulses compared to passive procrastinators [25]. In short, studies suggest that active procrastinators are more likely to display temperament- and character profiles that are associated with health and happiness.

Cognitive ability

Besides personality traits, research also focuses on cognitive factors contributing to academic procrastination, one of which is the need for cognition. Need for cognition is the tendency to like and engage in activities that require mental effort [26]. This need for cognition is negatively correlated with passive procrastination, and even though a positive correlation with active procrastination is expected, this has not yet been established [23, 27, 28]. Another cognitive ability that is relevant to procrastination is emotional intelligence (EI). EI refers to accurately expressing, interpreting, and regulating emotions and using them in decision-making [29]. Similar to the need for cognition, EI is negatively correlated with passive academic procrastination [30, 31]. In addition, active procrastinators show higher levels of EI than passive procrastinators [25]. As mentioned above, EI includes actively taking decisions, e.g. the decision to procrastinate, based on the monitoring of feelings to regulate these feelings [29]. This implies that the accurate monitoring of feelings is used to avoid mental distress in active procrastination but used less in passive procrastination [25]. Both the need for cognition and EI, thus, seem to play a role in academic procrastination, but associations differ for active and passive procrastination.

Sanchez-Ruiz *et al.* noted that personality traits and EI both affect academic procrastination [32]. Therefore, they investigated the effect of the trait EI, which is compromised of several personality traits that impact how an individual responds in emotional situations [33]. The result suggested that trait EI negatively predicts passive academic procrastination [32]. Concretely, individuals who have difficulties in dealing with stressful situations because of specific traits, e.g. self-discipline and self-efficacy, are more likely to procrastinate on academic work passively [32]. This research emphasises that academic procrastination is affected by the combination of both personality and cognitive abilities.

Task characteristics and theoretical frameworks on procrastination

Task aversiveness and the emotion-regulation theory

Academic procrastination is dependent on the characteristics of the task and/or activity that is to be procrastinated [1, 2, 11]. Unpleasant or aversive tasks are more likely to be avoided [1, 2, 11]. As simple as it may sound, not liking the task is one of the most often mentioned reasons for procrastination [34, 35]. The emotion-regulation theory posits that procrastination can result from avoidance of negative feelings brought on by an aversive task [36, 37]. Procrastination can be a consequence of prioritising a short-term good mood (i.e. avoiding the unpleasant task) over long-term beneficial outcomes [36, 37]. According to the emotion-regulation theory and the five-factor model, impulsive individuals with little self-discipline are more likely to procrastinate aversive tasks passively [36].

Expected rewards/punishments and the 2x2 theory

Another task characteristic that affects procrastination is composed of the future incentives, i.e. the expected rewards or punishments [1, 2, 11]. Both task aversiveness and future incentives are taken into account by the 2x2 theory [38]. One aspect of the 2x2 theory is that the motivation to fulfil a task can be either approach- or avoidance-based [38]. An approach-based strategy implies that a task is completed because of its future rewards, while for an avoidance-based strategy, the main driver to accomplish a task is to avoid a punishment [38]. Goal-orientated subjects with an approach-based strategy (i.e. aiming to reach a certain level of competence) were less likely to use procrastination as a way to avoid aversive tasks [38]. Therefore, procrastination in goal-orientated subjects may be applied not to regulate an aversive task's negative emotions but to enhance performance via active procrastination [38]. The 2x2 model, thus, considers the effects of task aversiveness and future incentives and allows for a better distinction between active and passive procrastination compared to the previous theory.

Time to rewards/punishments and the temporal motivation theory

In addition, academic procrastination is highly dependent on the time to rewards or punishments [1, 2, 11]. Rewards and punishments have a greater influence on our decisions when the consequences are more immediate versus when they are in the future [1]. The temporal motivation theory focuses on how future incentives and time to incentives affect procrastination [Equation 1] [2, 11, 39].

$$Outcome\ utility = \frac{Expectancy\ x\ Value}{1 + Sensitivity\ to\ delay\ x\ Delay}$$

Equation 1

Expectancy refers to the perceived chance that a reward can be obtained or punishment can be avoided [39]. Value refers to how much this outcome is worth to the individual [39]. Motivation to

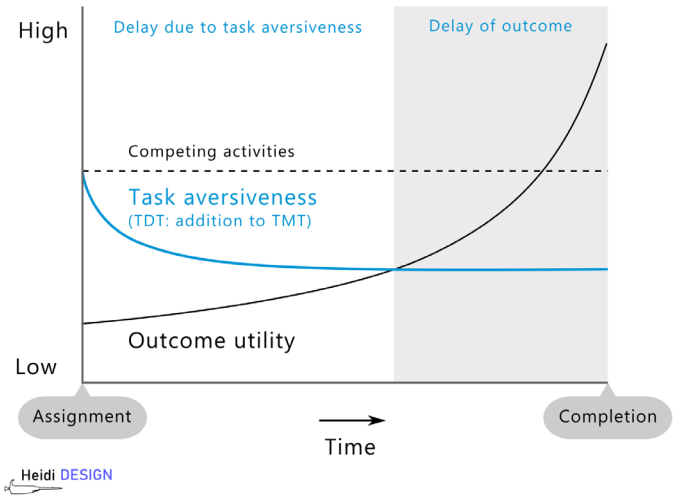

Figure 1: *Procrastination of a task explained by the temporal motivation theory (TMT) and temporal decision model (TDT – additional blue lines). This figure was created by combining Figure 1 of Steel et al. [1] and Figure 2 of Zhang et al. [11].*

fulfil a task (outcome utility) increases when an individual expects (expectancy) that a highly rewarded outcome (value) will be obtained [39]. An essential aspect of the temporal motivation theory is that everything depends on timing [39]. Motivation decreases when there is relatively much time until the reward or punishment will be obtained (delay) and when one is sensitive to this delay (sensitivity to delay) (Figure 1) [39]. The temporal motivation theory, thus, moves the focus from task aversiveness to (time to) future incentives.

Temporal decision theory

Zhang *et al.* noted that none of the above-mentioned theories suffices to fully explain academic procrastination [11]. The temporal motivation theory mainly focuses on (the timing of) future rewards and punishments, but not so much on task aversiveness [11, 39]. The emotion-regulation theory and the 2x2 theory, on the other hand, do not fully cover the importance of timing in procrastination [11, 36-38]. Therefore, the temporal decision theory was developed in which the decision to act or procrastinate depends on the task itself and (time to) future incentives [11]. At every moment in time, motivation to fulfil a certain (aversive) task at that time point is weighed against its future rewards or punishments [Equation 2] [11].

The outcome utility parameter from the temporal decision theory corresponds to the temporal motivation model [Equation 1], focussing on how motivation to act increases based on the *future* incentives and time to future incentives [11, 39]. The task aversiveness parameter refers to how much a task is perceived as unpleasant by the individual *at the time being* [11]. Only when outcome utility outweighs task aversiveness, the decision to act will be made, and the task will no longer be passively procrastinated (Figure 1) [11].

In conclusion, several models on procrastination have been developed, focussing on different aspects of tasks, i.e. task aversiveness, future incentives, and time to future incentives. The temporal decision theory is the only model that integrates the effects of all task-level characteristics on procrastination, potentially providing insight into how academic procrastination arises.

$$Decision = \underbrace{\frac{Expectancy\ (outcome)\ x\ Value\ (outcome)}{1+Sensitivity\ to\ delay\ (outcome)\ x\ Delay\ (outcome)}}_{Outcome\ utility} - \underbrace{\frac{Expectancy\ (aversiveness)\ x\ Value\ (aversiveness)}{1+Sensitivity\ to\ delay\ (aversiveness)\ x\ Delay\ (aversiveness)}}_{Task\ aversiveness}$$

Equation 2

Neurological perspective on procrastination

Having discussed how the psychological factors are involved in academic procrastination, the next section of this article will address the underlying neurological aspects of academic procrastination, of which two brain regions are of particular interest: the limbic system and the prefrontal cortex (PFC) (Figure 2). Relevant structures of both these regions will be discussed first, after which the results of several studies regarding procrastination will be given.

The limbic system

The limbic system plays a vital role in emotions, memory, motivation, and pleasure [40]. The region contains several structures, among which the amygdala is especially relevant in procrastination [40, 41]. The amygdala is best known for its role as a threat or fear generator [40, 42]. It receives input from all senses and associates those senses with emotions [40, 42]. In simple terms: the amygdala warns you about the possible adverse effects of a particular action and is shown to be larger in procrastinators [40, 41].

The parahippocampal gyrus/cortex (PHC), another limbic structure known to play a role in episodic memory and future thinking, is also relevant in the context of procrastination [40, 43, 44]. Several studies observed that interindividual differences in procrastination are linked to altered spontaneous metabolism or activity in the PHC and the prefrontal cortex [11]. The effects of certain personality traits on procrastination, such as future time perspective, might be mediated by certain parahippocampal pathways [45]. Furthermore, the PHC may mediate task aversiveness, which plays a vital role in emotion regulation theory, the 2x2 model, and the temporal decision theory [11, 36-38]. Although the temporal decision theory states that the PHC modulates both task aversiveness as outcome utility, it is too early to specify the exact association between PHC and procrastination [11].

An additional relevant limbic structure is the anterior cingulate cortex (ACC) that connects to both the 'emotional' limbic system and the 'cognitive' PFC [40, 43, 46]. The ACC is a system that executes goal-oriented actions to attain rewards and avoid negative outcomes and is involved in making adjustments for temporal delays by evaluating potential costs and benefits [43]. It has a cognitive component located dorsally and an emotional component located ventrally [46].

The prefrontal cortex

The PFC is a part of the frontal lobe and manages executive functions, which are a set of neurological processes involved in cognitive control and self-regulation [47]. Executive functions are crucial for individuals to plan and finish tasks, and they generally refer to processes involved in controlling short-sighted and goal-oriented behaviour [47, 48].

Considering that the PFC has these fundamental effects, this region can either positively or negatively affect competencies such as self-control, planning, decision-making, and problem-solving [47, 48].

These cognitive functions are complex; thus, it is unlikely that merely one brain region is responsible for them [47]. Nevertheless, evidence has shown that the PFC is of considerable importance in performing executive functions [47].

Each of the subregions of the PFC is suspected to be associated with slightly different aspects of cognition [47]. There is no clear consensus on these PFC subregions; however, standard demarcations include the dorsolateral, the dorsomedial, the ventrolateral, the ventromedial, and the orbitofrontal PFC [47]. The dorsolateral PFC is suggested to manage cognitive processes like planning and working memory [47, 49]. It is mainly involved in problem-solving and directing and maintaining attention to a task [47, 49]. Therefore, the dorsolateral PFC could play a role in several of the psychological theories mentioned before.

Whereas the dorsolateral PFC mainly contributes to executive functioning and cognitive control, the ventromedial PFC is assumed to be mainly involved in integrating signals from many brain regions [47, 49]. It receives information from several brain structures, including the amygdala, and is sensitive to the reward associated with a certain stimulus [50]. Furthermore, the ventrolateral PFC seems to be involved in response inhibition, which is a crucial executive function referring to the suppression of actions that are considered inappropriate in a given circumstance and interfere with goal-driven behaviour [51]. Lastly, the orbitofrontal PFC is closely related to limbic structures, including the amygdala and ACC, and is, thus, assumed to be relevant concerning the ability to make decisions based on emotional information [43, 47, 52]. The orbitofrontal PFC delivers inputs to the ACC with regard to the value of outcomes of certain goals [43, 52].

Neural mechanisms underlying procrastination

As stated before, procrastination results from an interaction between the limbic system, including the amygdala and the prefrontal cortex. Schlüter *et al.* examined the neural basis of interindividual differences in action control and procrastination [41]. The brains of 264 healthy individuals (mainly university students between 18 and 35 years old) were examined using MRI, which revealed that procrastination positively correlates with the grey matter volume of the amygdala [41]. According to the authors, the amygdala is responsible for fear-motivation behaviour [41]. In situations where a decision has to be made, the amygdala helps determine whether certain stimuli or conditions can be considered a threat [41]. In this respect, the authors suggested that individuals with a larger amygdala might more strongly weigh previous negative experiences, resulting in more concern for a possible negative outcome [41]. These negative experiences might have more power over decision-making, leading to procrastination to avoid undesirable consequences [41]. Alongside a larger amygdala volume, the study also linked procrastination to weaker connectivity between the amygdala and the dorsal ACC, which is essential in self-control [41]. However, it is unknown whether people who procrastinate have larger amygdala volume to start with or whether this has developed over time due to other factors. This lack of known causality has to be taken into account when interpreting these results.

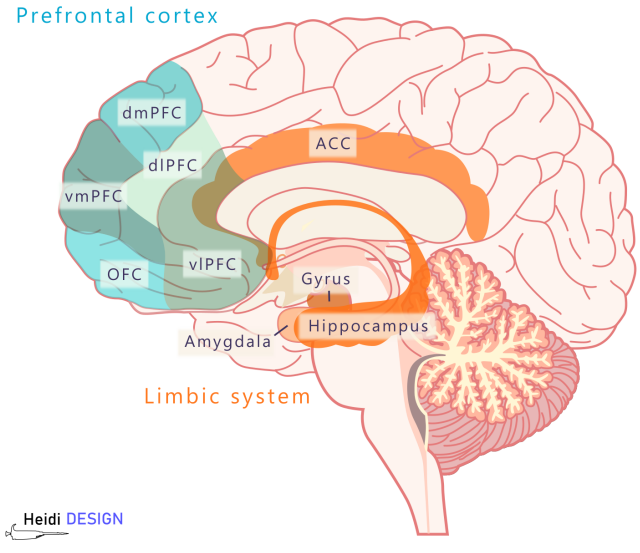

Figure 2: *Overview of brain regions relevant in terms of procrastination. The limbic system includes the amygdala, parahippocampal cortex (PHC), and anterior cingulate cortex (ACC). The prefrontal cortex (PFC) is divided into the dorsomedial PFC, the dorsolateral PFC, the ventromedial PFC, the ventrolateral PFC, and the orbitofrontal PFC.*

In addition to the amygdala, other brain structures are implicated in procrastination as well. Zhang *et al.* showed that procrastination has a positive correlation with the activity of the ventromedial PFC and PHC; a negative link was observed with the activity of the anterior PFC [53]. These results suggest that procrastination might be related to an overactive default mode network, which is a set of brain areas that show activity when individuals are not focused on the external environment (i.e. when resting, dreaming, or being unfocused) [53]. The researchers suggest that in individuals with a high procrastination tendency this network might interferes with the prefrontal cortex that is responsible for executive function, which leads to the higher tendency to procrastinate a task [53].

In a more recent study, Chen *et al.* used a sample of 688 subjects to explore the brain morphological characteristics of procrastination in both brain size and shape [54]. Several advanced brain imaging techniques were used to link procrastination to the grey matter volume and grey matter density of the brain [54]. A positive correlation was found between procrastination and the grey matter volume of the ACC and the insular cortex and PHC [54]. It turned out that the grey matter volume of the dorsolateral PFC was negatively linked to procrastination [54]. Procrastination was also positively associated with grey matter density of the ACC, ventromedial PFC, and CT complexity of orbitofrontal PFC [54]. In other words, it was found that the brain morphological features mentioned above can be considered as strong predictors for procrastination [54]. The authors described three brain subsystems to clarify the neural components related to procrastination. These are the self-control network (including the dorsolateral PFC and ACC), the emotional regulation network (including the orbitofrontal PFC and insular), and the episodic network (including the ventromedial PFC and PHC) [54].

Whether and how these brain networks interact and influence procrastination was elucidated in a more recent study performed by the same researchers [55]. In addition, this study aimed to capture neural biomarkers of procrastination using white matter microstructures and network features [55]. A positive association was found between limbic white matter tracts and procrastination [55]. Furthermore, the study revealed that the interconnection of the white matter of the frontoparietal and limbic systems is linked to procrastination. This outcome shows the role of interaction between the self-control system (ruled by the frontoparietal system) and the emotional process system (ruled by the limbic system) in procrastination [55]. In sum, several limbic and prefrontal regions are

involved in the concept of academic procrastination, which can be viewed as a result of interaction between these structures.

Conclusion

Procrastination can be viewed from a psychological and neurological point of view. Psychologically speaking, inconsistent results in previous research can be partly solved by dividing academic procrastination into two types: passive and active procrastination. Four models to frame the role of personality in procrastinators have been described, and the most important personality traits involved in general academic procrastination are impulsivity and little self-control, whereas extraversion and emotional stability seem to be predictors of active academic procrastination only. Cognitive factors, such as the need for cognition and EI, were negatively correlated with passive procrastination. Research also demonstrated that task characteristics influence procrastination. Tasks aversiveness seems to have a higher occurrence in tasks that are experienced as unpleasant. Finally, procrastination seems also to be dependent on the expected reward or punishment and the time at which these can be expected, as explained by the temporal motivation and temporal decision theory.

At a neurological level, procrastination has been positively linked to a larger volume of the amygdala and a weaker connection to the ACC. Research has also found that procrastination might depend on the activity of the ventromedial PFC and PHC. Thus, various subregions of the limbic system and the prefrontal cortex are relevant for the neurological understanding of academic procrastination. In this vein, procrastination might be a result of constant interaction between these two systems. The limbic system overrides the prefrontal cortex, causing procrastination; a universal affliction that is still of high interest in the neurological and psychological field.

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References

1. Steel, P. The nature of procrastination: a meta-analytic and theoretical review of quintessential self-regulatory failure. *Psychological bulletin* **133**, 65-94 (2007).
2. Steel, P. & Klingsieck, K. Academic Procrastination: Psychological Antecedents Revisited. *Australian Psychologist* **51**, 36-46 (2016).
3. Zhang, Y.*, et al.* Self-efficacy for self-regulation and fear of failure as mediators between self-esteem and academic procrastination among undergraduates in health professions. *Advances in health sciences education : theory and practice* **23**, 817-830 (2018).
4. Ozer, B.U.*, et al.* Exploring academic procrastination among Turkish students: possible gender differences in prevalence and reasons. *The Journal of social psychology* **149**, 241-257 (2009).
5. Grunschel, C.*, et al.* Exploring reasons and consequences of academic procrastination: An interview study. *European Journal of Psychology of Education* **28**(2012).
6. Patrzek, J.*, et al.* Academic Procrastination: The Perspective of University Counsellors. *International Journal for the Advancement of Counselling* **34**(2012).
7. Klassen, R.*, et al.* Academic procrastination of undergraduates: Low self-efficacy to self-regulate predicts higher levels of procrastination. *Contemporary Educational Psychology* **33**, 915-931 (2008).
8. Morris, P. & Fritz, C. Conscientiousness and procrastination predict academic coursework marks rather than examination performance. *Learning and Individual Differences* **39**(2015).
9. Chu, A.H. & Choi, J.N. Rethinking procrastination: positive effects of "active" procrastination behavior on attitudes and performance. *The Journal of social psychology* **145**, 245-264 (2005).
10. Choi, J.N. & Moran, S.V. Why not procrastinate? Development and validation of a new active procrastination scale. *The Journal of social psychology* **149**, 195-211 (2009).
11. Zhang, S.*, et al.* To do it now or later: The cognitive mechanisms and neural substrates underlying procrastination. *Wiley interdisciplinary reviews. Cognitive science* **10**, e1492 (2019).
12. Mccrae, R.R. & Costa, P.T., Jr. Validation of the five-factor model of personality across instruments and observers. *Journal of personality and social psychology* **52**, 81-90 (1987).
13. Poropat, A.E. A meta-analysis of the five-factor model of personality and academic performance. *Psychological bulletin* **135**, 322-338 (2009).
14. Cloninger, C.R.*, et al.* A psychobiological model of temperament and character. *Archives of general psychiatry* **50**, 975-990 (1993).
15. Cloninger, C.R. *Feeling good: The science of well-being*, (Oxford University Press, New York, NY, US, 2004).
16. Johnson, J.L. & Bloom, A.M. An analysis of the contribution of the five factors of personality to variance in academic procrastination. *Personality and Individual Differences* **18**, 127-133 (1995).
17. Schouwenburg, H.C. & Lay, C.H. Trait procrastination and the Big-five factors of personality. *Personality and Individual Differences* **18**, 481-490 (1995).
18. Van Eerde, W. A meta-analytically derived nomological network of procrastination. *Personality and Individual Differences* **35**, 1401-1418 (2003).
19. Watson, D.C. Procrastination and the five-factor model: a facet level analysis. *Personality and Individual Differences* **30**, 149-158 (2001).
20. Lay, C.H. Trait procrastination, agitation, dejection, and self-discrepancy. in *Procrastination and task avoidance: Theory, research, and treatment.*, Vol. 97-112 (Plenum Press, New York, NY, US, 1995).
21. Lay, C.H. Trait procrastination and affective experiences: Describing past study behavior and its relation to agitation and dejection. *Motivation and Emotion* **18**, 269-284 (1994).
22. Kim, S.*, et al.* Procrastination, personality traits, and academic performance: When active and passive procrastination tell a different story. *Personality and Individual Differences* **108**, 154-157 (2017).
23. Zhou, M. The role of personality traits and need for cognition in active procrastination. *Acta Psychologica* **199**, 102883 (2019).
24. Cloninger, C.R. & Zohar, A.H. Personality and the perception of health and happiness. *Journal of affective disorders* **128**, 24-32 (2011).
25. Zohar, A.H.*, et al.* Active and passive procrastination in terms of temperament and character. *PeerJ* **7**, e6988-e6988 (2019).
26. Cacioppo, J.*, et al.* Dispositional Differences in Cognitive Motivation: The Life and Times of Individuals Varying in Need for Cognition. *Psychological bulletin* **119**, 197-253 (1996).
27. Sarmány Schuller, I. Procrastination, need for cognition and sensation seeking. *Studia Psychologica* **41**, 73-85 (1999).
28. Laethem, S.*, et al.* Personality Correlates of the Melbourne Conflict Decision-Making Styles: Contribution of Need for Cognition and Need for Closure. *SSRN Electronic Journal* (2003).
29. Salovey, P. & Mayer, J.D. Emotional Intelligence. *Imagination, Cognition and Personality* **9**, 185-211 (1990).
30. Deniz, M.*, et al.* An Investigation of Academic Procrastination, Locus of Control, and Emotional Intelligence. *Educational Sciences: Theory and Practice* **9**(2009).

31. Wan, H.C., *et al.* Understanding non-work presenteeism: Relationships between emotional intelligence, boredom, procrastination and job stress. *Personality and Individual Differences* **65**, 86-90 (2014).
32. Sanchez-Ruiz, M.J. & El Khoury, J. A Model of Academic, Personality, and Emotion-Related Predictors of University Academic Performance. *Frontiers in psychology* **10**, 2435 (2019).
33. Petrides, K., *et al.* The Location of Trait Emotional Intelligence in Personality Factor Space. *British journal of psychology (London, England : 1953)* **98**, 273-289 (2007).
34. Anderson, E.M. The relationships among task characteristics, self-regulation and procrastination. *ProQuest Information & Learning* (2001).
35. Kachgal, M., *et al.* Academic Procrastination Prevention/ Intervention: Strategies and Recommendations. *Journal of Developmental Education* **25**, 14-24 (2001).
36. Sirois, F. & Pychyl, T. Procrastination and the Priority of Short-Term Mood Regulation: Consequences for Future Self. *Social and Personality Psychology Compass* **7**, 115–127 (2013).
37. Sirois, F.M. Absorbed in the moment? An investigation of procrastination, absorption and cognitive failures. *Personality and Individual Differences* **71**, 30-34 (2014).
38. Strunk, K.K., *et al.* Development and validation of a 2×2 model of time-related academic behavior: Procrastination and timely engagement. *Learning and Individual Differences* **25**, 35-44 (2013).
39. Steel, P. & König, C. Integrating Theories of Motivation. *Academy of Management Review* **31**, 889-913 (2006).
40. Rajmohan, V. & Mohandas, E. The limbic system. *Indian journal of psychiatry* **49**, 132-139 (2007).
41. Schlüter, C., *et al.* The Structural and Functional Signature of Action Control. *Psychological science* **29**, 1620-1630 (2018).
42. Balleine, B.W. & Killcross, S. Parallel incentive processing: an integrated view of amygdala function. *Trends in neurosciences* **29**, 272-279 (2006).
43. Rolls, E.T. The cingulate cortex and limbic systems for emotion, action, and memory. *Brain structure & function* **224**, 3001-3018 (2019).
44. Aminoff, E.M., *et al.* The role of the parahippocampal cortex in cognition. *Trends in cognitive sciences* **17**, 379-390 (2013).
45. Liu, P. & Feng, T. The effect of future time perspective on procrastination: the role of parahippocampal gyrus and ventromedial prefrontal cortex. *Brain imaging and behavior* **13**, 615-622 (2019).
46. Heilbronner, S.R. & Hayden, B.Y. Dorsal Anterior Cingulate Cortex: A Bottom-Up View. *Annual review of neuroscience* **39**, 149-170 (2016).
47. Funahashi, S. & Andreau, J.M. Prefrontal cortex and neural mechanisms of executive function. *Journal of physiology, Paris* **107**, 471-482 (2013).
48. Carlén, M. What constitutes the prefrontal cortex? *Science (New York, N.Y.)* **358**, 478-482 (2017).
49. Nejati, V., *et al.* The role of dorsolateral and ventromedial prefrontal cortex in the processing of emotional dimensions. *Scientific reports* **11**, 1971 (2021).
50. Kim, H., *et al.* Overlapping responses for the expectation of juice and money rewards in human ventromedial prefrontal cortex. *Cerebral cortex (New York, N.Y. : 1991)* **21**, 769-776 (2011).
51. Chikazoe, J. Localizing performance of go/no-go tasks to prefrontal cortical subregions. *Current opinion in psychiatry* **23**, 267-272 (2010).
52. Rolls, E.T., *et al.* The orbitofrontal cortex: reward, emotion and depression. *Brain communications* **2**, fcaa196 (2020).
53. Zhang, W., *et al.* Identifying the Neural Substrates of Procrastination: a Resting-State fMRI Study. *Scientific reports* **6**, 33203 (2016).
54. Chen, Z., *et al.* Brain Morphological Dynamics of Procrastination: The Crucial Role of the Self-Control, Emotional, and Episodic Prospection Network. *Cerebral cortex (New York, N.Y. : 1991)* **30**, 2834-2853 (2020).
55. Chen, Z., *et al.* Neural markers of procrastination in white matter microstructures and networks. *Psychophysiology* **58**, e13782 (2021).

SCIENCE COMMUNICATION IN THE 21ST CENTURY: RESPONSIBILITIES, SOCIAL MEDIA, AND FAKE NEWS?

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Interview

Do you also have a relative still believing that diet products cause cancer? Or that vaccinations will cause autism? And how many of your friends have asked you whether the COVID-19 virus was indeed created in a lab? Science myths like these can be sturdy and widespread, even in this era of information abundance. While information has never been this accessible and fast-spreading, the same applies to misinformation. Especially in light of the ongoing pandemic, it is often stated that "science communication is more important now than ever" [1]. But is there really an ever-increasing urgency to communicate science more and better? And how should this be addressed?

The communication of science

Science can be communicated in many forms and for many reasons. Any activity, skill, media, or dialogue may be used to invoke public awareness, enjoyment, interest, opinion-forming, or understanding of science [2]. While scientific discoveries are expected to contribute to the growth and welfare of society, one could say that "a scientific discovery is only as good as its communication" [3]. Plain facts alone often do not bring about changes in behaviour, and only a well-informed society can make meaningful choices about the benefits and risks of scientific developments [4, 5]. The importance of science communication has become even more apparent during the ongoing pandemic, where public misbeliefs about topics such as vaccination may hinder the efforts to control the pandemic [6]. While a shift from conventional to online and social media is enabling a rapid spread of misinformation, it also offers opportunities for science communicators to reach a wide public [7]. In order to discuss these challenges and opportunities, RAMS interviews two enthusiastic science communicators, Shweta Mahajan and Anne van Kessel. Mahajan, currently a master's student in Molecular Mechanisms of Disease, communicates science through her podcast "Science with Shweta" and recently also started a Youtube channel and Instagram page for this purpose. Van Kessel is a freelance science journalist, communicating science through a variety of platforms, including news articles, television, radio, and books.

Science journalism

The majority of scientists seem to endorse the importance of science communication. For example, a recent survey among 3,700 researchers in Sweden showed that nine out of ten researchers were

Shweta Mahajan, MSc (Master's student molecular mechanisms of disease)

Anne van Kessel, MSc (Science journalist)

positive about communicating their science to the public, with the most important reason being that the results should be utilised by society [8]. Yet, not all scientists communicate science (effectively), and, at the same time, not all science communicators are scientists. Van Kessel points out that science journalism, which is a branch of science communication, is performed by journalists, not by active scientists. After all, journalism should be unbiased and independent [9]. "Of course, you could still discuss whether these journalists should have some background in that scientific area as well or whether the job could also be done by general journalists. Some may say that not having this background knowledge will help you in identifying with the reader and [identifying with] what the reader wants to know. At the same time, having this [scientific] background as a journalist will help you to better understand what you are writing about. You will be able to read and understand the original papers better, and you will know if something is truly groundbreaking."

The role of scientists

While science journalism may be reserved for objective journalists, active scientists can communicate their own research in many other ways. Mahajan believes that scientists themselves indeed have an important responsibility to fulfil. "I think that communication merely between science communities belongs to the old days. Right now, scientists should really be reaching out to the people. They [the scientists] play a big role in passing on information as they know the scientific basis. They can bust the myths existing in people's minds and in society." However, not all scientists might actually have the motivation to communicate their research or lack the right skills or time to do so. "I think it is a combination of all those factors," says van Kessel. "It does not fit every scientist. You need to have a certain feeling for it, and you have to enjoy it. It really is a specific skill and not everyone can do it naturally, but I do believe that anyone can learn it. Yet, scientists and physicians are already busy. They should get the time to engage in science communication activities. Having to do all that in your spare time, does not make it very attractive, of course."

So it seems that in order to let scientists fulfil their role in communicating science, they should be provided with the right motivations, skills, and time. "It is more and more often a requirement for science funds to show how you communicate your research to the general public and how you will engage the public," confirms Van Kessel. "In that sense, scientists are stimulated to be involved in science communication. At the Radboud Institute for Health Sciences, for example, all starting PhD candidates also get an introduction on science communication, which includes training on how to sell your science." Mahajan agrees that the right training and rewards are important and emphasises that this could already start at the level of the student: "We should already try to engage students more through such education; tell them why science communication is important and to reach out. Because they will be the next generation of scientists."

The rise of social media

In today's society, social media play an important role in the way people interact and communicate with each other. Mahajan and Van Kessel both see the potential of using social media in science communication. Mahajan mentions, "If we are already using it for all other purposes, why do we not make the best out of it." "I see it as a chance; you can discuss your results or research with a broad audience", says Van Kessel. Around 2013, widespread adoption of social media was not yet present among scientists, and it was mainly used for communicating and networking with other scientists [10]. Currently, social media are being used more and more by scientists from all disciplines to communicate their work [11]. Van Kessel mentions that individual researchers are different in their social media use. "Some researchers really like it and want to invest time in it, whereas for others it is not their cup of tea and [they] do not invest the time." Twitter seems to be the preferred medium as it has the potential for quick and broad engagement [12]. If the scientist has a sufficient number of followers, the reach will increase exponentially, breaking the barrier between scientists and the public [13, 14]. "Right now, [when you search for a scientist], they have their own website but they also have their own Twitter account, and a lot of them are really active on Twitter," mentions Mahajan. Van Kessel notes, "There are several accounts, like NLwetenschap and NLzorg, that let doctors and researchers show their daily life. That is really nice for the public to follow." To reach young adults, Facebook seems to be more effective than Twitter [15]. "A lot of young people are on social media, and if we want to reach them, then it [social media] is a good platform," says Mahajan. She also notices a shift in her audience: "There is a lot of difference between now and three years ago. Many more people are reaching out to me and following other people that are into science communication."

However, as every coin has two sides, there are downsides to the use of social media. Scientists should be aware of their role on social media, according to Van Kessel. "If a doctor publishes a politically sensitive post on their personal account, while he/she is an employee of the Radboudumc, for example, people will make a connection. So you have to carefully decide what to put on your social media." The rapid nature of social media makes this even more important as it is difficult to rectify mistakes as they rapidly spread to a wide audience [12].

Misinformation and fake news

Social media use is increasing and with it the fear of misinformation and fake news. Misinformation in the public can disconnect the public opinion from the scientific consensus [16]. With an increasingly polarised political environment and changes in how information is shared by the media, misinformation and fake news are a real threat [16]. The World Economic Forum has recently called on scientists to provide the public with factual information via social media to prevent and decrease fear of COVID-19 among the public in the light of the current pandemic [17].

Unfortunately, there is little research on the prevalence and impact of fake news [18]. On Twitter, fake news travels far more rapidly than true information [19]. Automated bots can magnify the spreading of fake news by liking, sharing, and searching for information [18]. One effort estimated that 9 to 15 per cent of Twitter accounts were bots [20]. Van Kessel says: "I think that it is hard to prevent fake news from being distributed because there is no limit to what people can post on the internet." People can become misinformed due to a lack of understanding of science, conspiratorial beliefs, and selective exposure [16]. "[As a science communicator], you should be wary of spreading fake news. So, your sources should be on point and you should have spoken to an expert who was not involved in the research," Van Kessel notes. Hype and overclaims in press releases and other scientific communication might lead to misinformation of the public [16]. According to Van Kessel, every press release is prone to overclaims. "With a press release, the scientists and PR department want to bring the news into the media. So, in some way they are selling the research, making it prone to exaggerations."

Conclusion

Scientists are aware of the importance of science communication, yet not all scientists do communicate their science. While the specific area of science journalism is reserved to objective journalists,

scientists can reach out to the public and share their results and research themselves. However, lack in, for example, motivation, time, and skills seem to be discouraging scientists. Over the last few years, social media are increasingly used by scientists to communicate about science. Although this trend provides opportunities, social media should be used with caution. With the increase in social media use, misinformation and fake news are also becoming more of a problem. The risk of disconnection with the public opinion is present, making it more important than ever for scientists to share the correct information. Above all, 'a scientific discovery is only as good as its communication' [3].

Recommendations on science communication

Recommendations from the authors/RAMS editors

Science Cafe Nijmegen - Monthly meeting with scientists in the Irish Pub named Shamrock.

Museum for Anatomy and Pathology - Museum within the Faculty of Medicine concerning the human anatomy and pathology.

Recommendations from Shweta Mahajan

Richard Dawkins - The Selfish Gene

Stephen Hawking - A Brief History of Time

Stuff You Should Know - A science podcast that explains everything in layman terms

Science Vs - A casual podcast busting science myths

Recommendations from Anne van Kessel

NRC Podcast - Onbehaarde apen over wetenschap

Tijs Stehmann - Dokter ik las in de krant dat...

Ionica Smeets - Het exacte verhaal

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References

1. Science communication is more important than ever [internet]. Theconversation.com. 2020 [cited: April 11, 2021]; available from: https://theconversation.com/science-communication-is-more-important-than-ever-here-are-3-lessons-from-around-the-world-on-what-makes-it-work-147670
2. Burns, T.W., *et al.* Science Communication: A Contemporary Definition. *Public Understanding of Science* **12**, 183-202 (2003).
3. Abraham, G. The Importance of Science Communication. *Metallography, Microstructure, and Analysis* **9**, 3-4 (2020).
4. What science communicators can learn from listening to people [internet]. Theconversation.com. 2014 [cited: April 11, 2021]; available from: https://theconversation.com/what-science-communicators-can-learn-from-listening-to-people-25087
5. Bubela, T., *et al.* Science communication reconsidered. *Nature Biotechnology* **27**, 514-518 (2009).
6. Marco-Franco, J.E., *et al.* COVID-19, Fake News, and Vaccines: Should Regulation Be Implemented? *Int J Environ Res Public Health* **18**, 744 (2021).
7. Nisbet, M.C. & Scheufele, D.A. What's next for science communication? Promising directions and lingering distractions. *American Journal of Botany* **96**, 1767-1778 (2009).
8. Researchers' views on communication and open science in sweden – a summary [internet]. Vetenskap & Allmänhet. 2019 [cited: April 11, 2021]; available from: https://v-a.se/2019/09/researchers-views-on-communication-and-open-science-in-sweden/
9. Elliott, K.C. Science Journalism, Value Judgments, and the Open Science Movement. *Frontiers in Communication* **4**(2019).
10. Collins, K., *et al.* How Are Scientists Using Social Media in the Workplace? *PLOS ONE* **11**, e0162680 (2016).
11. Ke, Q., *et al.* A systematic identification and analysis of scientists on Twitter. *PLOS ONE* **12**, e0175368 (2017).
12. Hunter, P. The growth of social media in science. *EMBO reports* **21**, e50550 (2020).
13. Côté, I.M., *et al.* Scientists on Twitter: Preaching to the choir or singing from the rooftops? *FACETS* **3**, 682-694 (2018).
14. Smith, A. "Wow, I didn't know that before; thank you": How scientists use Twitter for public engagement. *Journal of Promotional Communications* **3**, 320-339 (2015).
15. Hargittai, E., *et al.* How Do Young Adults Engage With Science and Research on Social Media? Some Preliminary Findings and an Agenda for Future Research. *Social Media + Society* **4**, 2056305118797720 (2018).
16. Scheufele, D.A. & Krause, N.M. Science audiences, misinformation, and fake news. *Proceedings of the National Academy of Sciences* **116**, 7662-7669 (2019).
17. Anonymous. Accurate science communication is key in the fight against COVID-19.
18. Lazer, D., *et al.* The science of fake news. *Science* **359**, 1094-1096 (2018).
19. Vosoughi, S., *et al.* The spread of true and false news online. *Science* **359**, 1146-1151 (2018).
20. Varol, O., *et al.* Online Human-Bot Interactions: Detection, Estimation, and Characterization. (2017).

ZEBRAS OF MEDICINE:
ATOPIC DERMATITIS AND HYPER IGE SYNDROME, WHEN TO SUSPECT PRIMARY IMMUNODEFICIENCY?

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Abstract

Insight

Atopic dermatitis (AD) is the most frequent cause of eczema and is associated with allergies, increased risk for skin infections, and high blood serum IgE levels. Atopic dermatitis considerably overlaps with the clinical presentation of the Hyper IgE syndromes (HIES), a set of rare primary immunodeficiencies. Especially in young children, diagnosis of HIES can be difficult considering that many characteristic signs of HIES, other than eczema, only develop at a later stage. Early diagnosis is beneficial for managing HIES as it allows for early initiation of targeted treatment and early consideration for hematopoietic stem cell transplantation. Thus, differentiating AD and HIES in young children is of considerable importance. This article delineates the overlap and differences between AD and HIES, with a particular focus on the mechanisms behind predispositions to infections, that can help raise suspicion of HIES in patients presenting with AD-like eczema.

KEYWORDS: Eczema, recurrent infections, HSCT, STAT3, DOCK8

Dermatitis, also often referred to as eczema, is a very common condition that is most often caused by atopic dermatitis (AD) [1]. AD often first presents in childhood, and many patients outgrow it before adolescence [2]. In the Netherlands, the general population prevalence is 3%, but for children between the ages of 0 and 10, the prevalence ranges from 6-12% [3]. AD is a chronic inflammatory skin disease and is likely caused by a combination of skin barrier dysfunction, immune system dysfunction, and environmental factors [2]. AD is associated with, among others, itching that causes sleep interruptions, an increased risk of allergies, and an increased risk of infections [2]. While AD can be challenging to manage in some cases, the condition and its associated manifestations are generally non-life-threatening [4]. However, the chronic eczema that is present in AD can also be a symptom of a set of rare primary immunodeficiency disorders (PIDs): the Hyper-IgE syndromes (HIES) [1]. PIDs are inborn errors of the immune system, and, currently, more than 350 different disorders are recognised [5]. In the Netherlands, the five-year incidence of PID is 6.8 in 100,000 [6]. Early diagnosis of a PID is of the utmost importance for better management of the condition and, in some cases, allows for life-saving haematopoietic stem cell transplantation (HSCT) [7, 8]. While chronic eczema is a symptom of many PIDs, HIES and severe AD can be especially hard to distinguish due to overlap in clinical presentation [1, 9].

Currently, five types of HIES have been described, each with a different gene affected; *STAT3, DOCK8, PGM3, CARD11,* and *ZNF431* [7]. *STAT3* deficiency and *DOCK8* deficiency are the most well-characterised HIES; thus, this paper will primarily focus on these types of HIES [7, 9]. The HIES are generally characterised by a triad of AD-like eczema, elevated IgE levels, and recurrent infections [7]. Furthermore, other symptoms, such as skeletal and dental abnormalities, are associated with the condition, dependent on the type of HIES [7]. Nevertheless, while the triad symptoms are incredibly common in HIES patients, they are very unspecific and can especially be confused with severe AD [9, 10]. Therefore, the triad symptoms are unsuitable for the diagnosis of HIES [9]. The elevated IgE levels to which the HIES thank their name are also highly prevalent in AD [11]. Furthermore, AD patients have an increased risk of infections [12, 13]. However, the difference in type and severity of the infections that are to be expected in HIES versus those to be expected in AD can help distinguish these two diseases [9, 10]. The official diagnosis of HIES is based on the National Institutes of Health HIES scoring system that can successfully distinguish between HIES and AD in older children [10]. However, this scoring system is not always successful at diagnosing HIES in younger children, as many symptoms might only arise at a later age [9]. HIES patients often have a considerably large diagnostic delay; for example, in the Netherlands, diagnosis on average takes 10.5 years from the first presentation of symptoms [6]. Overall, a diagnostic delay is caused by a combination of the rarity of the condition, the often nonspecific symptoms that are easily confused with AD, and the specific symptoms only arising at a later age [9-11].

This review compares AD and HIES with a focus on their associated infections and underlying disease mechanisms to help determine a suspicion of HIES at a younger age, thereby improving early diagnosis. Additionally, differences in treatment between AD and HIES are discussed.

Disease mechanism

The key to distinguishing AD from HIES is through understanding the underlying mechanisms causing the infectious complications in these conditions. Patients with AD have an increased chance of skin infections, likely due to various risk factors associated with AD [13]. Currently, the exact cause of AD is incompletely understood but likely involves genetic factors, a dysfunctional immune response, and environmental factors [14-16]. In AD, the combination of these three factors can work together to impair many aspects of the defences of the skin barrier leading to an increased risk of skin infections [2]. The skin defends against infections through four main barriers: the physical barrier, the chemical barrier, the immunological barrier, and the microbiome barrier [14]. In AD, there are many mechanisms through which the skin barrier is thought to become impaired. A few of these mechanisms will be further outlined.

The physical barrier of the skin consists of the stratum corneum (the outermost layer of the skin) and the tight junctions between epithelial cells [14]. When the physical skin barrier becomes dysfunctional, for example due to genetic predisposition, the skin barrier will more easily be penetrated by an allergen or irritant [2]. The allergens or irritants, when processed by an antigen-presenting cell in the skin,

can trigger Th2 cells to produce type two inflammatory cytokines [2, 17]. This inflammatory response can, in turn, further damage the physical skin barrier, worsening skin barrier degradation, and, additionally, can cause an impaired chemical barrier [14]. An essential feature of the chemical barrier of the skin is secreted antimicrobial peptides, which help prevent infection [18]. The type two inflammatory response contains IL-4 and IL-13, which have been shown to cause a reduction of antimicrobial peptide production in the skin, leading to an increased risk of skin infection [19, 20]. Not only a defective skin barrier but likely also a change in the microbiome can lead to inflammation in the skin. Skin affected by AD is very susceptible to colonisation by *Staphylococcus aureus (S. aureus)*; a recent meta-analysis found that 70% of AD patients carried *S. aureus* [21]. Superantigens produced by *S. aureus* can enhance type two inflammation, causing a breakdown of the skin barrier and a reduction of antimicrobial peptide secretion, which, in turn, further increases the risk of infection [22].

Skin infections in AD are primarily bacterial infections with *S. aureus*, but other infections occur as well [21]. While *S. aureus* can be found on healthy skin, the combination of a dysfunctional skin barrier and high rates of *S. aureus* colonisation likely predispose AD patients to skin infections with *S. aureus* [23]. Furthermore, AD skin is more susceptible to viral infection with the herpes simplex virus type 1 (HSV-1), which causes eczema herpeticum (EH) and is experienced by 3% of patients [24]. Exposure to HSV-1 is common, but only a small subset of AD patients experience EH, indicating that other environmental or host factors are necessary for the development of EH [24]. Finally, AD patients also have an increased risk for fungal infections of the skin, likely caused by skin barrier defects, allowing usually harmless fungal species to colonise and cause infection [25].

Patients with HIES have a more generally increased risk of infections because genetic mutations cause a dysfunctional immune system [7]. HIES patients are highly susceptible to bacterial and fungal infections, which will often be recurrent and difficult to treat [9]. In both STAT3-HIES and DOCK8-HIES, a combination of deficiencies of Th17 cells and antibodies appear to be very important for this susceptibility [7]. Th17 cells are a type of T-helper cells that, through the secretion of IL-17 and IL-22, stimulate epithelial cells to secrete chemokines and antimicrobial peptides [26, 27]. STAT3-HIES patients have low Th17 cell counts, whereas DOCK8-HIES patients are suspected of having malfunctioning Th17 cells [9]. This failure of innate immunity in epithelial cells likely is the cause of increased susceptibility to bacterial and fungal infections of the skin and airways [9, 28]. Furthermore, HIES patients have a lack of high-affinity antigen-specific antibodies [29, 30]. In STAT3-HIES patients, this might be caused by reduced somatic hypermutation for several antibody types leading to impaired affinity maturation, but reports remain conflicting [29]. DOCK-HIES patients likely have a defective T-cell and B-cell interaction, again leading to impaired affinity maturation [31, 32]. The lack of high-affinity antigen-specific antibodies means that HIES patients have an impaired adaptive immune response, further explaining the recurrency and severity of infections.

DOCK8-HIES patients have also been shown to be more vulnerable to viral infections of the skin; however, this is uncommon in STAT3-HIES [30]. DOCK8-HIES patients are thought to have defects in both the innate and adaptive immune response to viruses. Firstly, natural killer (NK) cells with suppressed DOCK8 show defective cytotoxicity [33]. Secondly, DOCK8 deficient NK and T cells have a predisposition to undergo cell death when migrating through tissue, likely limiting the number of cytotoxic cells that could reach virally infected skin [34]. Overall, the defective response of NK and T cells likely allows for poor control of viral pathogens in patients with DOCK8-HIES [30]. Overall, both AD and HIES patients have an increased susceptibility to infections; however, due to the differences in underlying physiopathology, the type of infection, as well as the predominance of certain pathogens, differ. Infectious complications in patients with AD are usually limited to the skin and can be caused by bacteria, viruses, and fungi [2]. In rare cases, usually in severe AD, a skin infection can lead to systemic complications and hospitalisations [13]. A common cause of systemic complications is EH, which can include encephalitis and septic shock [35]. Furthermore, systemic complications from bacterial infections can include osteomyelitis and septic arthritis [13]. In HIES patients, infectious complications of the skin are also common [9, 10]. In STAT3-HIES patients, skin infections are usually caused by bacteria or fungi, while in DOCK8-HIES patients, viral skin infections are often found [9-11]. Importantly, and in contrast with AD patients, the spectrum of infections seen in HIES patients is not limited to the skin [30, 36]. While, like in AD, HIES patients are susceptible to skin infections with *S. aureus*, HIES patients are also susceptible to invasive *S. aureus* infections. Patients with HIES often experience infections of the airways, including upper respiratory infections, pneumonia, and bronchitis [30, 36]. Furthermore, infectious complications such as osteomyelitis, internal abscesses, and sepsis are common [10, 30]. Thus, infection susceptibility in AD is linked to the damaged skin barrier, and skin infections are expected, while in HIES infection susceptibility is linked to a dysfunctional immune system and infections of both the skin and invasive infections, such as those affecting the airways or bones, are expected.

Diagnosis

Multiple diagnostic criteria for AD are in use but involve a combination of the main feature of itchy skin with some minor features, including a history of dry skin and a personal or family history of allergies [37]. AD predisposes patients to skin infections and likely also to some extracutaneous infections, such as ear infections and urinary tract infections, although the mechanism behind this remains unclear [38, 39]. Furthermore, AD is strongly associated with the development of allergies, such as allergic rhinitis, asthma, and food allergies [40]. Thus, the clinical presentation of AD includes not only dermatitis but also infections and allergies. HIES patients have a strong overlap in presentation with AD patients. Dermatitis, high serum IgE levels, and a predisposition to skin infections are all seen in both HIES and AD patients [9, 11, 13]. Furthermore, DOCK8-HIES patients often present with allergies, but allergies are also strongly associated with AD [11, 30, 40]. This strong overlap begs the question of when to suspect HIES and refer the patient to a specialist.

There are several findings that should raise the suspicion of HIES in a patient presenting with AD. In the case of STAT3-HIES, these are often skeletal, dental, and connective tissue abnormalities [10]. These clinical features present as bone fractures without apparent trauma, pathological rendition of primary teeth, scoliosis, hyperextensible joints, and characteristic facial features [7, 9, 10]. HIES patients are also at increased risk for benign tumours and malignancy [9, 30]. Family history can also help identify HIES. Strong indicators are a family history of HIES, unexplained family member death, and, especially in DOCK8-HIES, consanguinity [9, 10, 30]. Overall, these findings help distinguish HIES from AD. However, young children might not yet display skeletal, dental, and connective tissue findings or malignancy [9]. Therefore, to identify HIES in young children, it is crucial to consider infections as an indicator of HIES.

In patients with HIES, infections are known to be severe, recurrent, and sometimes even life-threatening due to their impaired immune system [7, 30]. Serious infectious complications such as internal

abscesses and sepsis are common, and, considering the recurrent feature of HIES, patients experience multiple infections per year, often lasting for multiple weeks [10, 41]. As AD patients are susceptible to skin infections, skin infections should only be considered an indicator of HIES if associated with infectious complications or if they are recurrent [9]. DOCK8-HIES patients are particularly vulnerable to viral skin infections, and, in contrast to AD, which is mainly associated with EH caused by *HSV-1*, DOCK8-HIES patients often experience infections with a wide variety of viruses, including *varicella-zoster, molluscum contagiosum*, and *human papillomaviruses* [11, 30, 43]. Thus, recurrent viral infections by multiple viruses are an indicator of DOCK8-HIES [30]. Furthermore, the HIES susceptibility to severe and recurrent airway infections is not found in AD [38]. Thus, the occurrence of multiple pulmonary infections per year that need treatment with antibiotics is a good indicator of HIES [9-11]. In turn, these recurrent pulmonary infections in HIES patients can lead to the development of bronchiectasis [10, 43].

Overall, while AD patients are also at increased risk of skin infections, infections that should raise suspicion of HIES include recurrent and severe bacterial and fungal skin infections, recurrent invasive infections, and, in the case of DOCK8-HIES, recurrent and severe viral skin infections. When children with AD-like eczema present with these HIES infection patterns, a follow-up should take place where the child is evaluated for other signs of HIES [9]. The National Institutes of Health HIES scoring guideline followed by genetic testing can be used to confirm a HIES diagnosis [7]. Thus, symptoms of AD and HIES can overlap, but important indicators for HIES include recurrent and invasive infections, skeletal, dental and soft tissue abnormalities, malignancy, and family history (figure 1).

Treatment

Treatment of AD is focused on maintaining skin barrier function. As transepidermal water loss is an essential aspect of skin barrier dysfunction, patients with AD are recommended to hydrate and moisturise their skin daily [4]. When regular hydration and moisturisation fails to improve dermatitis, topical anti-inflammatory medications, such as topical corticosteroids, can improve skin barrier functions [4]. Usually, bacterial infections and fungal infections are easily treated with oral antibiotics and topical anti-fungal creams, respectively [2, 25]. Suspicion of eczema herpecticum should be quickly treated with systemic anti-viral medication to prevent serious complications [35]. In cases of severe AD, where previously mentioned treatment has failed to control severe dermatitis, phototherapy or systemic immunosuppressants can be considered [4].

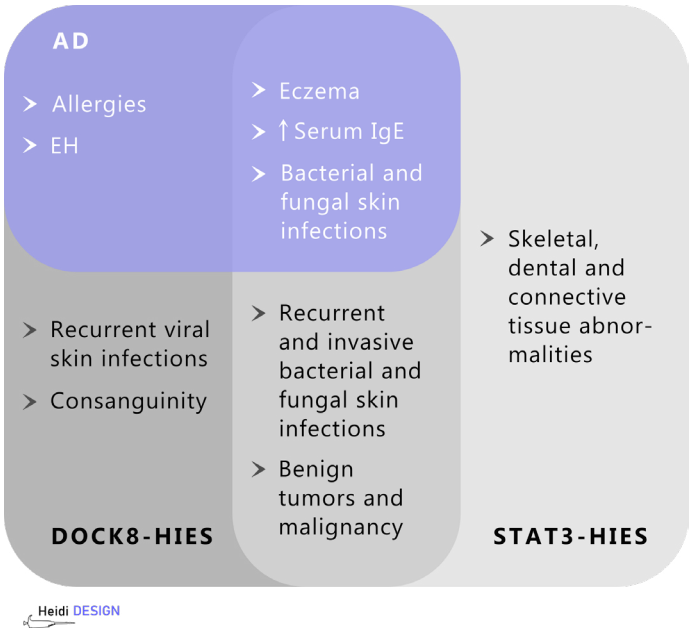

***Figure 1**: Symptoms and complications of atopic dermatitis (AD), STAT3-HIES, and DOCK8-HIES. HIES = Hyper-IgE syndromes, EH = eczema herpeticum.*

Management of HIES focuses on the prevention and treating of infections. Prophylaxis treatment with anti-bacterial, anti-viral, and anti-fungal medication can help prevent these infections [9, 30]. Additionally, an HSCT treatment can be recommended as high morbidity and mortality are associated with the condition [30]. However, HSCTs necessitate the availability of a suitable donor and are not without risks, meaning this treatment is not always a viable option and must be carefully considered [30]. Initial reports of HSCT in STAT3-HIES patients were doubtful about its effectiveness as no reduction of IgE levels took place [44]. However, a recent long-term follow up found that HSCT in all eight STAT3-HIES patients greatly reduced infections and even completely abolished skin infections [45]. The effectiveness of HSCT in DOCK8-HIES patients has been reported in many case reports and, recently, in a larger retrospective study of 71 patients by Aydin *et al.* [44-46]. Patients were found to have improved or abolished eczema (99%) and greatly reduced or abolished pulmonary infections (93%) [46].

Diagnosing HIES at a young age is incredibly important, as it not only allows prophylaxis initiation and quick treatment of infections to help prevent long-lasting damage but also allows for the consideration of treatment with an HSCT at a young age. Performing HSCT at a young age means that the patient is less likely to have already developed long-lasting damage from previous infections or to have developed malignancy [41]. Furthermore, a case report of HSCT in two siblings with DOCK8-HIES found that the patient who received an HSCT at eight months old had more improved symptoms than the patients who received an HSCT at eight years old, indicating that perhaps transplantation at a young age is beneficial for HIES patients [9]. However, an ideal age range for HSCT in DOCK8-HIES patients could not be determined by Aydin *et al.* and likely requires analysis of much larger patient groups [46].

Conclusion

All in all, while AD and HIES have significant overlap in their clinical presentation, there are several observations that should raise suspicion of HIES. At a young age, primarily frequent and severe infections of the skin and airways set apart the more strongly immunological compromised HIES patient from the AD patient. Early diagnosis of HIES is crucial as it allows for screening for infection, initiation of prophylaxis, and consideration of HSCT, which can greatly reduce the morbidity and mortality associated with these conditions.

Acknowledgements

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References

1. Mortz, C.G., *et al.* It looks like childhood eczema but is it? *Clinical and Experimental Allergy* **49**, 744-753 (2019).
2. Brar, K.K., et al. Strategies for Successful Management of Severe Atopic Dermatitis. *The Journal of Allergy and Clinical Immunology: In Practice* **7**, 1-16 (2019)
3. Verboom, P., *et al.* The cost of atopic dermatitis in the Netherlands: An international comparison. *British Journal of Dermatology* **147**, 716-724 (2002).
4. Boguniewicz, M., *et al.* Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. *Annals of Allergy, Asthma and Immunology* **120**, 10-22.e12 (2018).

5. Picard, C., *et al.* International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol* **38**, 96-128 (2018).
6. Jonkman-Berk, B.M., *et al.* Primary immunodeficiencies in the Netherlands: National patient data demonstrate the increased risk of malignancy. *Clinical Immunology* **156**, 154-162 (2015).
7. Al-Shaikhly, T. & Ochs, H.D. Hyper IgE syndromes: clinical and molecular characteristics. *Immunology and Cell Biology* **97**, 368-379 (2019).
8. Hagl, B., *et al.* Somatic alterations compromised molecular diagnosis of DOCK8 hyper-IgE syndrome caused by a novel intronic splice site mutation. *Scientific Reports* **8**, 1-10 (2018).
9. Hagl, B., *et al.* Key findings to expedite the diagnosis of hyper-IgE syndromes in infants and young children. *Pediatric Allergy and Immunology* **27**, 177-184 (2016).
10. Schimke, L.F., *et al.* Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *Journal of Allergy and Clinical Immunology* **126**, 611-617.e611 (2010).
11. Kasap, N., *et al.* A set of clinical and laboratory markers differentiates hyper-IgE syndrome from severe atopic dermatitis. *Clinical Immunology* **223**, 108645-108645 (2021).
12. Narla, S. & Silverberg, J.I. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Annals of Allergy, Asthma and Immunology* **120**, 66-72. e11 (2018).
13. Wang, V., *et al.* The infectious complications of atopic dermatitis. *Annals of Allergy, Asthma and Immunology* **126**, 3-12 (2021).
14. Kuo, I.H., *et al.* The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol* **131**, 266-278 (2013).
15. Cabanillas, B. & Novak, N. Atopic dermatitis and filaggrin. *Curr Opin Immunol* **42**, 1-8 (2016).
16. Kantor, R. & Silverberg, J.I. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Review of Clinical Immunology* **13**, 15-26 (2017).
17. Elias, P.M. & Steinhoff, M. "Outside-to-inside" (and now back to "outside") pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol* **128**, 1067-1070 (2008).
18. Kopfnagel, V., *et al.* Expression of antimicrobial peptides in atopic dermatitis and possible immunoregulatory functions. *Curr Opin Allergy Clin Immunol* **13**, 531-536 (2013).
19. Ong, P.Y., *et al.* Endogenous Antimicrobial Peptides and Skin Infections in Atopic Dermatitis. *New England Journal of Medicine* **347**, 1151-1160 (2002).
20. Berdyshev, E., *et al.* Lipid abnormalities in atopic skin are driven by type 2 cytokines. *JCI insight* **3**, 1-15 (2018).
21. Totté, J.E.E., *et al.* Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. *British Journal of Dermatology* **175**, 687-695 (2016).
22. Kim, J., *et al.* Interactions between atopic dermatitis and staphylococcus aureus infection: Clinical implications. *Allergy, Asthma and Immunology Research* **11**, 593-603 (2019).
23. Boguniewicz, M. & Leung, D.Y.M. Recent insights into atopic dermatitis and implications for management of infectious complications. *Journal of Allergy and Clinical Immunology* **125**, 4-13 (2010).
24. Leung, D.Y.M. Why is eczema herpeticum unexpectedly rare? *Antiviral Research* **98**, 153-157 (2013).
25. Thammahong, A., *et al.* The clinical significance of fungi in atopic dermatitis. *International Journal of Dermatology* **59**, 926-935 (2020).
26. Liang, S.C., *et al.* Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *Journal of Experimental Medicine* **203**, 2271-2279 (2006).
27. Zheng, Y., *et al.* Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nature Medicine* **14**, 282-289 (2008).
28. Kane, A., *et al.* STAT3 is a central regulator of lymphocyte differentiation and function. *Current Opinion in Immunology* **28**, 49-57 (2014).
29. Van De Veen, W., *et al.* Impaired memory B-cell development and antibody maturation with a skewing toward IgE in patients with STAT3 hyper-IgE syndrome. *Allergy: European Journal of Allergy and Clinical Immunology* **74**, 2394-2405 (2019).
30. Biggs, C.M., *et al.* DOCK8 deficiency: Insights into pathophysiology, clinical features and management. *Clinical Immunology* **181**, 75-82 (2017).
31. Randall, K.L., *et al.* Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production. *Nature Immunology* **10**, 1283-1291 (2009).
32. Jabara, H.H., *et al.* DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. *Nature Immunology* **13**, 612-620 (2012).
33. Ham, H., *et al.* Dedicator of Cytokinesis 8 Interacts with Talin and Wiskott-Aldrich Syndrome Protein To Regulate NK Cell Cytotoxicity. *The Journal of Immunology* **190**, 3661-3669 (2013).
34. Zhang, Q., *et al.* DOCK8 regulates lymphocyte shape integrity for skin antiviral immunity. *Journal of Experimental Medicine* **211**, 2549-2566 (2014).
35. Seegraber, M., *et al.* Recurrent eczema herpeticum - a retrospective European multicenter study evaluating the clinical characteristics of eczema herpeticum cases in atopic dermatitis patients. *J Eur Acad Dermatol Venereol* **34**, 1074-1079 (2020).
36. Mogensen, T.H. STAT3 and the Hyper-IgE syndrome. *Jak-Stat* **2**, e23435-e23435 (2013).
37. Ponsford, M.J., *et al.* Hyper-IgE in the allergy clinic––when is it primary immunodeficiency? *Allergy: European Journal of Allergy and Clinical Immunology* **73**, 2122-2136 (2018).
38. Serrano, L., *et al.* Association between atopic dermatitis and extracutaneous bacterial and mycobacterial infections: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology* **80**, 904-912 (2019).
39. Ren, Z. & Silverberg, J.I. Association of Atopic Dermatitis with Bacterial, Fungal, Viral, and Sexually Transmitted Skin Infections. *Dermatitis* **31**, 157-164 (2020).
40. Zheng, T., *et al.* The atopic march: Progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy, Asthma and Immunology Research* **3**, 67-73 (2011).
41. Aydin, S.E., *et al.* DOCK8 Deficiency: Clinical and Immunological Phenotype and Treatment Options - a Review of 136 Patients. *Journal of Clinical Immunology* **35**, 189-198 (2015).
42. Gennery, A.R., *et al.* Bone marrow transplantation does not correct the hyper IgE syndrome. *Bone Marrow Transplantation* **25**, 1303-1305 (2000).
43. Harrison, S.C., *et al.* Hematopoietic Stem Cell Transplantation Resolves the Immune Deficit Associated with STAT3-Dominant-Negative Hyper-IgE Syndrome. *Journal of Clinical Immunology* (2021).
44. Barlogis, V., *et al.* Successful allogeneic hematopoietic stem cell transplantation for DOCK8 deficiency. *Journal of Allergy and Clinical Immunology* **128**, 420-422.e422 (2011).
45. Ghosh, S., *et al.* Haploidentical stem cell transplantation in DOCK8 deficiency - Successful control of pre-existing severe viremia with a TCRaß/CD19-depleted graft and antiviral treatment. *Clinical Immunology* **152**, 111-114 (2014).
46. Aydin, S.E., *et al.* Hematopoietic Stem Cell Transplantation as Treatment for Patients with DOCK8 Deficiency. *The Journal of Allergy and Clinical Immunology: In Practice* **7**, 848-855 (2019).

INTERNSHIVERS*

Guus Brand[1]

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Column

Guus Brand is a medical student at the Radboud University in Nijmegen and our standard columnist. He writes about peculiarities or striking events he encounters during his study program. This column discusses stress-related complaints amongst medical master's students, followed by a response from *rector magnificus* of Radboud University Han van Krieken, also a professor of pathology.

Last March, I finally received the news that I can start my clinical rotations in November 2022. Every medical student has to perform clinical internships at varying departments in different hospitals for three years in order to achieve their master's degree. However, when I received my starting date, I began to tremble at what lies ahead. Medical interns are expected to work at least 38 hours a week and, as good grades are a must for every medical student, invest additional time studying to keep performing at a high level. Furthermore, travel times can reach up to three hours a day, and many students have to work a part-time job next to their education since the student grants have been abolished. Lastly, because these years are supposed to be the time of one's life, we should meet friends, go clubbing, travel, and generally live our lives to the fullest. Paul Roodenburg, a general practitioner and teacher at the Amsterdam UMC, puts it as follows: "It seems socially unacceptable not to be busy " [1]. As a student currently trying to do all this while struggling to maintain a manageable schedule, I hope you can understand my reservations.

And I am not the only one. A 2015 questionnaire amongst medical interns shows that 17.8 per cent meet the criteria to be diagnosed with a burnout [2]. As this study was carried out in 2015, one can only imagine what it is like at this moment with the COVID-19 pandemic still raging. The lockdown and other measures taken to contain the virus may have a massive impact on the mental health of students, causing them to feel lonely and depressed and lowering their educational performances [3]. Outreach programmes are being set up but do not affect the performance anxiety that already exists around clinical rotations [4].

So what can be done to help students cope with this pressure and anxiety? In my opinion, the first changes should be made in the minds of students. Both recently graduated doctors and senior medical professionals that I spoke with confirm that your resume regarding your university period is not even close to being as important as many medical students think. What is important is that you are responsible, knowledgeable, and, most of all, passionate. And yes, grades and experience in related fields do play a part, but this seems to be marginal according to the people I spoke with. The road to becoming the medical specialist most of us aspire to be is long and hard. However, working yourself to the bone, while trying to study, maintaining a busy social life, and doing extracurricular tasks to jack up your resume, should not be the way to go. Just making it through medical school and having a good and informative time should be the goal, and it should be enough.

Secondly, I think an addition to the curriculum might be beneficial. Verweij *et al*. state that medical residents with high baseline levels of emotional exhaustion benefit from mindfulness-based stress reduction [5]. Not every resident benefits from this programme because not every resident experiences high baseline levels of stress. Personally, I believe that these results can be extrapolated to medical internships. The expectations and hours are roughly the same, with the only differences being responsibility and payment. Why not make similar comprehensive and accessible mindfulness programmes an optional part of the curriculum? Not all medical interns have high baseline levels of stress, so they should be optional, but they should be there nonetheless. With these changes, I believe we can make a significant impact on the amount of pressure and anxiety that medical interns experience, and hopefully provide the world with a group of more "mentally stable" doctors in the future.

Guus Brand

References

1. Van Twillert M. De Co staat altijd aan. *Arts in Spe* 2017 May 23. *Translated quote*
2. Conijn M, Boersma HJMV, Van Rhenen W. Burn-out bij Nederlandse geneeskundestudenten. *NTVG* **159**, A8255P (2015).
3. Struijs S. *De geestelijke gezondheid van studenten tijdens de COVID-19 pandemie*. Caring Universities. 2020 August 19.
4. Landelijke Werkgroep Studentenwelzijn. *Handreiking studentenwelzijn in corona-tijd*. 2020 July.
5. Verweij, H., van Ravesteijn, H., van Hooff, M.L.M. et al. Mindfulness-Based Stress Reduction for Residents: A Randomized Controlled Trial. *J GEN INTERN MED* **33**, 429–436 (2018).

**This column aims to highlight the personal perspective of a student. Therefore, the views and ideas expressed in this column are the own personal views of the columnist and do not necessarily reflect the view of RAMS. If you have any questions of comments regarding this column, contact the editorial board of RAMS.*

Be true to yourself

With much recognition I read the column of Guus Brand, bringing back memories about myself during clinical internships. I like to work hard but not for long, and I do need my sleep and relaxation. That was the case when I was a student and that is the case now. My first day at my first internship started at 8 am, so I had to be on my bike at 6:45 am. When I arrived at the morning report with a brand new white coat on, I was together with only one fellow intern instead of the normal four; we were welcomed by the head of internal medicine with the warning that we would have a hard time, since interns had to take on all the night shifts, so for us that meant to be on call every other night. Without thinking I replied that I would do no such thing, and a deep silence was in the room: such a remark was unheard of, but the professor said, "I understand, we are making another rotation scheme", and that was it. Later I realised that I could have been sent home, my behaviour was not fitting the culture. But I also felt: if that was the way it works, it would be without me. I have learned over the years that being true to myself and being honest about it almost always works.

As Guus writes, make choices and try to keep your stress level in control. Your period of clinical internships can be among the best times of your life, but it is heavy-duty, with many emotions (you may see the first person die in your hands, tell a child that he or she has cancer, you will make mistakes). This comes with responsibility: no parties, alcohol, or drugs the day before you are in the clinic; talk about your experiences, choose your leisure time carefully. Your real friends understand that your time in the clinic asks a lot from you, they will support you and understand that you cannot be at every party or get-together and that you need to be in bed on time. And yes, mindfulness may work for you; for me it was the bike ride to set my mind at peace. Guus, enjoy your clinical internships: you have the right mindset!

Han van Krieken

Han van Krieken, Prof, MD-PhD (Rector magnificus)

Additional reading sources

Are you intrigued by burnouts amongst medical students after reading this column? Have a look at the following articles selected by RAMS:

- Hansell, M., Ungerleider, R., Brooks, C., Knudson, M., Kirk, J. Ungerleider, J. Temportal Trends in Medical Student Burnout. *Fam Med* **51**, 399-404 (2019).
- Erschens, R., Keifenheim, K., Herrmann-Werner, A., Loda, T. Schwille-Kiuntke, J., Bugaj, T. Professional burnout among medical students: Systematic literature review and meta-analysis. *Med Teach* **41**, 172-183 (2019).

EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelor's!

We challenge you!

Question 1

Myasthenia gravis is a disease of the neuromuscular junction, caused by antibodies targeting the post-synaptic receptors. These receptors are needed for the transportation of electric nerve signals from the nerve to the muscle. Which type of medication will decrease the symptoms in patients with myasthenia gravis?

A. Acetylcholinesterase inhibitor
B. Acetylcholin receptor antagonist
C. Glutamate dehydrogenase inhibitor
D. Glutamate receptor antagonist

(Topic from Q6 MGZ Immune system, 2020)

Question 2

A couple has been trying to conceive for 17 months without success. The 30-year old woman has a regular cycle of 30 days. During ultrasound examination, the total antral follicle count is 12. There are no signs of uterine tube dysfunction. Her partner's semen has a total of 0.5 million moving sperm cells per ejaculation (VCM count). Which treatment is indicated?

A. Wait and see
B. Start with artificial insemination
C. Start with ovulation-induction
D. Refer the partner to the urologist

(Topic from Q8 MGZ Reproduction, 2019)

The answers to these questions can be found on page 29 in this journal.

COVID-19 VACCINES CURRENTLY UNDER CONDITIONAL MARKETING AUTHORISATION IN THE EUROPEAN UNION

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Abstract

Summary

A total of four vaccine candidates for Corona Virus Disease – 19 have been granted conditional marketing authorisation by the European Medicines Agency. These new vaccines have been designed, developed, and tested in as little as eleven months. Novel vaccination strategies, such as mRNA vaccines, have been employed by various pharmaceutical companies to create vaccines with an impressive level of efficacy. Thus far, the conditionally approved vaccines all have a high vaccine efficacy and display a generally favourable safety profile. However, as different phases of clinical development have been performed within one protocol and phase III trial follow-up has been relatively short, long-term effects for neither safety nor efficacy have been observed yet. Different dosing regimens, storage conditions, and mechanisms of action show that each Corona Virus Disease – 19 vaccine currently under conditional marketing authorisation can fill its own niche. The current vaccine landscape is volatile, and vaccination policies are frequently changing. The vaccines that have been granted conditional marketing approval must still undergo the rest of the European Medicines Agency regular marketing approval process but have reported results of early clinical trials and interim results of their various phase III trials. These data show a generally favourable safety profile and remarkable efficacy.

In the past year, the world as we know it has been changed by the arrival of Severe Acute Respiratory Syndrome – Corona Virus 2 (SARS-CoV-2) and the associated Corona Virus Disease – 19 (COVID-19). Currently, there is no designated cure for COVID-19. However, vaccination is a promising strategy to reduce the burden of COVID-19 on the individual and on society. A multitude of companies has spent the last year developing and testing vaccines for COVID-19. As of March 23rd, the vaccines conditionally approved for use in the European Union by the European Medicines Agency (EMA) are Comirnaty (BNT162b2), developed by Pfizer, BioNTech, and Fosun Pharma; Moderna COVID-19 Vaccine (mRNA-1273), developed by Moderna, BARDS, and NIAID; AZD1222, developed by The University of Oxford and AstraZeneca; and COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S), developed by Janssen Vaccines [1, 2]. In total, thirteen vaccines have been granted (conditional) approval for emergency use in various countries around the world [1]. Next to this, a large number of other vaccine candidates are still in various stages of (pre-)clinical development [1].

The Netherlands has started to vaccinate various groups of the population on January 6th, 2021. As of March 28th, an estimated 1,688,490 people have received their first injection, and 690,062 people have received their second injection in The Netherlands [3]. So far, The Netherlands have only used the Comirnaty, Moderna, and AstraZeneca vaccines [3]. It is important to note that the policy regarding which vaccines are used and what dosing regimens are used may change in the future. The information included in this review is accurate as of April 2nd, 2021. The aim of this narrative review is to generate an overview of the mechanisms of action, safety and efficacy concerns, and general differences between the four COVID-19 vaccines currently in use in the European Union.

Current COVID-19 vaccines

BNT162b2/ Comirnaty

Comirnaty, or BNT162b2, is the COVID-19 vaccine developed by Pfizer, BioNTech, and Fosun Pharma and was the first COVID-19 vaccine administered outside of a study setting [4]. The vaccine uses a single strand, 5'-capped, non-replicating, nucleoside-modified mRNA, encoding the surface spike protein of SARS-CoV-2 that has been slightly modified to retain a prefusion conformation (structure of the protein before cell infection), which makes the first contact with the antigen easier (table 1) [4-7]. The mRNA is encapsulated in lipid nanoparticles to prevent RNA degradation and allow for cellular uptake [4, 5]. Once the vaccine is administered intramuscularly, the mRNA is taken up into host cells, where it is translated into the viral spike protein and incorporated into the cell membrane [4, 5]. Subsequently, the expression of the spike protein on the cell membrane will act as a pathogen-associated molecular pattern (PAMP) for immune cells, and an adaptive immune response is launched [4-6]. Successful vaccination with Comirnaty will result in circulating neutralising antibodies and cellular immunity against the spike protein [4-6]. As the spike protein is similar across multiple strains of coronaviruses, using the spike protein as a vaccination target may decrease the impact of random mutations or different variants of SARS-CoV-2 [4]. Finally, vaccination with Comirnaty resulted in higher neutralising antibodies than a normal immune response to SARS-CoV-2 would [4].

The vaccine is supplied in a frozen multiuse vial and must be thawed and diluted before a dose can be administered intramuscularly [7]. Each vial must be kept at -80°C and contains six vaccine doses after dilution; one dose contains 30 µg of mRNA [4-7]. Full immunisation requires two doses, spread at least 21 days apart [5-7]. Comirnaty reaches full effect seven days after the second injection [5, 6]. The second injection of Comirnaty can, thus far, not be substituted with a different vaccine, as data on combining vaccines are lacking [7].

Comirnaty is currently indicated for use in all adolescents and adults over the age of 16 unless one of the risk criteria, such as a suspected or proven allergy to one of the components of the vaccine, is present [7]. In December 2020, a publication of the largest clinical trial concerning the safety and efficacy of BNT162b2 was published, containing data of 42,448 participants, of which 18,556 received both doses of BNT162b2, and 18,530 received both doses of saline

placebo [5]. BNT162b2 recipients more often reported pain at the site of injection, while other local reactions such as redness and swelling were reported in similar frequency compared to placebo, after both the first and second dose [5, 6]. The local reactions were mostly mild-to-moderate in nature and were resolved in one to two days [5]. Systemic events, such as fatigue, headache, and muscle pain, increased in prevalence after the second dose in the vaccine groups [5]. BNT162b2 recipients reported more adverse events (AEs) overall: 27% versus 12% reported any AEs; 21% versus 5% reported treatment-related AEs (vaccine group versus placebo group, respectively) [5]. Most of these AEs are short-lasting, mild effects. In total, four treatment-related serious AEs were reported in the BNT162b2 group [5]. Overall, BNT162b2 displays an acceptable short-term safety profile, and safety monitoring will continue for two years after the administration of the second dose in the vaccine group [5].

For the efficacy of the vaccine, the trial observed the onset of COVID-19 in its participants seven days or more after the second dose of the regimen [5]. In those with no indication of a prior or current infection with SARS-CoV-2, only 8/18,556 cases of COVID-19 were observed in the vaccine group, compared to 162/18,530 among those in the placebo group, yielding a vaccine efficacy (VE) of 95.0% (95% Confidence Interval (CI): 90.0-97.9) [5]. This VE is comparable across age- and ethnic groups [5].

mRNA-1273/Moderna

The Moderna vaccine or mRNA-1273 is similar to the Comirnaty vaccine. mRNA-1273 is also a single strand, 5'-capped mRNA vaccine encapsulated in lipid nanoparticles, encoding the full-length spike protein of SARS-CoV-2 locked into the prefusion-stabilised position (table 1) [8, 9]. However, mRNA-1273 is dosed with 100 µg of mRNA per dose, is only indicated for persons above 18 years old, contains up to ten doses per supplied flask, and can be kept at a higher temperature of -25°C to -15°C [8, 9]. Similarly to Comirnaty, the vaccine is administered intramuscularly. The dosing regimen consists of two injections into the same arm, spread 28 days apart [9]. The second dose of mRNA-1273 can also not be substituted by a different vaccine due to the lack of data with combined schedules [8].

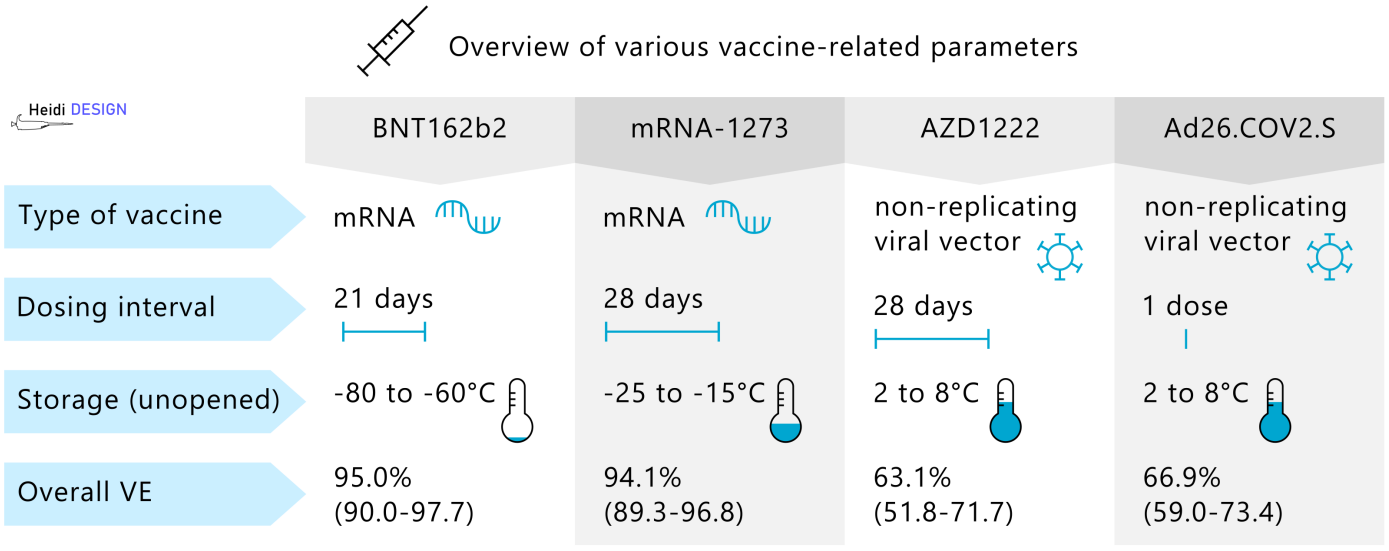
A large trial recruited adults over 18 years old with no known history of a SARS-CoV-2 infection but who were at risk of contracting a SARS-CoV-2 infection or its related disease COVID-19 [9]. A total of 30,420 participants were enrolled in the study and randomised at a 1:1 ratio between treatment and placebo groups. 14,134 and 14,073 participants in the treatment and saline placebo group, respectively, completed the full study thus far and were included in the analysis. AEs were recorded for 28 days following the injections. Local AEs were reported in 88.6% of the treatment group versus 18.8% in the placebo group after the second injection [9]. Pain at the site of the injection was reported as the main adverse event in the majority of the cases (86.0%) [9]. The incidence of solicited systemic AEs increased between the first and the second dose in the treatment group (54.9% vs 42.2% after the first compared to 79.4% vs 36.5% after the second, treatment vs placebo) [9]. The severity of the solicited adverse effects also increased after the second dose in the treatment group (16.5% to 38.1% grade II and 2.9% to 15.8% grade III of all reported solicited AEs) [9]. Any treatment-related AEs were reported in 8.2% and 4.5% of participants in the treatment group versus the placebo group, respectively [9]. Severe treatment-related AEs were reported in 0.5% of the treatment group versus 0.2% of the placebo group [9].

VE was analysed 14 days after the second dose. Only 11/14,134 cases of COVID-19 were reported in the treatment group, compared to 185/14,073 cases in the placebo group [9]. This yields a VE of 94.1% (95% CI: 89.3-96.8) for preventing symptomatic COVID-19 cases compared with placebo [9]. The vaccine also appears to prevent severe COVID-19; the 30 severe cases that were reported throughout the study were all in the placebo group [9]. According to these results, mRNA-1273 seems to be an excellent addition to the vaccination programme with a very similar efficacy profile to Comirnaty.

AZD1222/AstraZeneca

AZD1222 consists of a viral vector originating from a chimpanzee containing a monovalent, recombinant, non-replicating adenovirus (ChAdOx1), encoding the full-length spike protein (table 1) [10, 11]. Unlike the Cormirnaty and Moderna mRNAs, the AstraZeneca adenovirus was not modified to lock the resulting spike protein in the prefusion conformation [10]. Unopened flasks of AZD1222 contain ten doses of vaccine and can be kept in the refrigerator for six months between temperatures of 2°C and 8°C [12]. Once opened, the flask can be kept at the same conditions but must be fully used within two days [12]. The dosing regimen consists of two intramuscular injections, spread 28 days apart, in adults over 18 years old [10, 11]. Both a one-dose regimen, as well as a two-dose regimen

Table 1: *Overview of various vaccine-related parameters. IM: intramuscular; VE: vaccine efficacy*



have been tested [10, 11]. Two different dose strengths have been tested as well, being 2.2·1010 viral particles (low) and 5·1010 viral particles (regular) per dose [10, 11].

A pooled analysis of four clinical trials, totalling 24,422 participants, examined the safety and efficacy of AZD1222 [11]. 17,178 participants were included in the primary efficacy analysis, which examined the incidence of virologically confirmed, symptomatic COVID-19 cases, identified 14 days or later after the second dose as the outcome measure [11]. The other participants were dosed only once or were lost to follow-up. AZD1222 has a VE of 66.7% (95% CI: 57.4-74.0) overall for the previously mentioned primary efficacy analysis [11]. A low dose plus standard dose regimen appeared to provide more protection (VE: 80.7% (95% CI: 62.1-90.2)) than two times the standard dose regimen (VE 63.1% (95% CI: 51.8-71.7)) [11]. However, this may have been the result of uneven sample sizes, as the former condition was only explored in one trial in the United Kingdom [10, 11]. The safety data were comparable between the vaccine groups and the control groups [11]. 0.9% of all participants in the vaccine group reported any severe adverse event, compared to 1.1% of all participants in the saline control group; severe nausea and myalgia were more common in the vaccine group [11]. Overall, AZD1222 did not seem to induce more AEs than the control group.

In the first weeks of March 2021, several countries, among which the Netherlands, had shortly suspended the use of the AZD1222 vaccine after a few dozen case reports of severe blood clotting following vaccination with AZD1222 surfaced, known as thrombosis with thrombocytopenia [13]. However, an in-depth investigation by the EMA stated that there is no link between vaccination with AZD1222 and an increased risk of blood clots [14]. Most countries have since resumed using AZD1222 again, albeit with an adjusted schedule where only people over the age of 60 are vaccinated. However, the debate surrounding the safety of the AZD1222 vaccine intensified at the end of March and start of April 2021, when the EMA released a document stating the clotting problem must be listed as a very rare side effect, but that the advantages of vaccination with AZD1222 still outweigh the risks of rare side effects [15].

Ad26.COV2.S/Janssen Vaccine

The Janssen Vaccine consists of an adenovirus type 26, encoding the full-length spike protein of SARS-CoV-2 (table 1) [16]. It is supplied in multiuse vials, containing five doses of vaccine containing 5·1010 viral particles each. The vaccine must be administered intramuscularly and is indicated for adults over 18 [16]. Different from the previously described vaccines, Ad26.COV2.S only has to be injected once [16]. Similarly to AZD1222, Ad26.COV2.S can be stored at temperatures between 2°C and 8°C, although it must be fully used within 6 hours of opening [16].

Currently, Johnson & Johnson is running two phase III trials for Ad26.COV2.S. The ENSEMBLE (COV3001, NCT04505722) and ENSEMBLE 2 (NCT04614948) examine the safety and efficacy of one- and two-dose regimens, respectively. The ENSEMBLE trial is currently ongoing and has closed recruitment. Data from the ENSEMBLE trial, which entails 44,325 participants, was used for conditional marketing authorisation of the one-dose regimen by the EMA on March 11th, 2021 [1]. The ENSEMBLE 2 trial is currently still recruiting participants.

The preliminary data from the ENSEMBLE trial showed an overall VE of 66.9% (95% CI: 59.03-73.40) 14 days after vaccination and 66.1% (95% CI: 55.01-74.80) 28 days after vaccination against any severity of COVID-19 [17]. However, this VE is higher when examining the severe cases of COVID-19 [17]. Fourteen days after vaccination, Ad26.COV2.S had a VE of 76% (95% CI: 54.56-89.09), and 28 days after vaccination, the VE rose to 85.4% (95% CI: 54.15-96.90) against severe cases of COVID-19 [17].

The American Food and Drug Administration (FDA) Emergency Use Authorisation (EUA) contains some information about the safety of Ad26.COV2.S. Solicited local AEs, such as injection site pain (58.6% vs 17.4%), injection site erythema (9.0% vs 4.3%), and injection site swelling (7.0% vs 1.6%) were reported more often in the vaccine group compared to the placebo group in the population aged 18-59, in the seven days following vaccine administration. The individuals aged 60 and up had a smaller discrepancy between the vaccine group and the placebo group for all local AEs: 33.3% vs 15.6% for injection site pain; 4.6% vs 3.2% for injection site erythema; and 2.7% vs 1.6% for injection site swelling in the vaccine group and control group, respectively. The vaccine group also scored higher in all categories of solicited systemic AEs, consisting of headache (reported by 44.4% vs 24.8%), fatigue (43.8% vs 22.0%), myalgia (39.1% vs 12.1%), nausea (15.5% vs 8.9%), fever (12.8% vs 0.7%), and use of antipyretic drugs or pain medication (26.4% vs 6.0%). The proportion of participants reporting unsolicited AEs was similar in both groups (13.1% in the vaccine group, 12.0% in the placebo group). Serious AEs, such as urticaria, blood clots, and seizures, were more common in the vaccine group but were so rare that this could thus far not be linked to the use of the Ad26.COV2.S vaccine. The safety profile was similar to a phase I and phase IIa trial, which had its data published in January 2021 [18]. Overall, the safety profile of Ad26.COV2.S was deemed sufficient, and Ad26.COV2.S was granted conditional marketing authorisation by the EMA.

Discussion

It is important to note that this review is based on short-term data, and the efficacy and safety profile of the vaccines may change over time. New, long-term safety concerns may arise after a longer time of observation. Additionally, it is known that the efficacy of other vaccines, such as influenza vaccines, wanes over time [19]. The median time since the final dose was about two months at the time of publishing of most phase III trials included here [5, 6, 9-11]. Next to this, there are no approved vaccines or medications for COVID-19 at the moment. The vaccines currently in use have only been granted conditional marketing authorisation. The companies behind the vaccines currently in use must continue submitting data on the process of manufacturing, safety, and efficacy of their product until the requirement for regular approval by the EMA is met. If serious side effects were to surface after a longer observation time, the regular approval could be denied, or the conditional marketing authorisation status can be revoked.

That being said, it is astonishing to realise that some of these novel vaccines have been designed, developed, and (partially) tested in as little as eleven months. This was made possible by the collaboration of health organisations, pharmaceutical companies, and universities. Major time was gained by blending clinical trial phases using multi-phase protocols (i.e., phase I and phase II, phase II and phase III) and the fast-tracked publishing of study results [20, 21]. Although the possibility of mRNA vaccines has been studied since the 1990s, COVID-19 is the first high profile case in which an mRNA vaccine was used [20-22]. The phase III trials of BNT162b2, mRNA-1273, and AZD1222 reported findings of early protection after the first dose [5, 6, 9-11]. As some countries are investigating a change in their dosing regimen by changing the second dose to 12 weeks after the first, instead of three to four weeks, this early protection may prove to be favourable.

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References

1. Craven, J. COVID-19 vaccine tracker. 2021 (Regulatory Affairs Professionals Society, 2021).
2. Anonymous. COVID-19 vaccines: authorised. 2021 (European Medicines Agency, 2021).
3. Anonymous. Cijfers COVID-19 vaccinatieprogramma. 2021 (Rijksinstituut voor Volksgezondheid en Milieu, Ministerie van Volksgezondheid, Welzijn en Sport, The Netherlands, 2021).
4. Lamb, Y.N. BNT162b2 mRNA COVID-19 Vaccine: First Approval. *Drugs* **81**, 495-501 (2021).
5. Polack, F.P.*, et al.* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* **383**, 2603-2615 (2020).
6. Walsh, E.E.*, et al.* Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* **383**, 2439-2450 (2020).
7. Anonymous. spc-comirnaty-inn-covid-19-mrna-vaccine.pdf. 2021 (Lareb, 2021).
8. Anonymous. COVID-19 Vaccine Moderna, INN-COVID-19 mRNA Vaccine (nucleoside modified). 2021 (Lareb, 2021).
9. Baden, L.R.*, et al.* Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine* **384**, 403-416 (2021).
10. Ramasamy, M.N.*, et al.* Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* **396**, 1979-1993 (2021).
11. Voysey, M.*, et al.* Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* **397**, 881-891 (2021).
12. Anonymous. COVID-19 Vaccine AstraZeneca, COVID-19 Vaccine (ChAdOx1-S [recombinant]). 2021 (Lareb, 2021).
13. Wise, J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ* **372**, n699 (2021).
14. Mahase, E. Covid-19: AstraZeneca vaccine is not linked to increased risk of blood clots, finds European Medicine Agency. *BMJ* **372**, n774 (2021).
15. Anonymous. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 2021 (European Medicines Agency, 2021).
16. Anonymous. Johnson & Johnson COVID-19 Vaccine Authorized by U.S. FDA For Emergency Use - First Single-Shot Vaccine in Fight Against Global Pandemic. 2021 (Johnson & Johnson, 2021).
17. Anonymous. COVID-19 Vaccine Janssen, INN-Ad26.COV2-S, recombinant. 2021 (European Medicines Agency, 2021).
18. Sadoff, J.*, et al.* Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. *N Engl J Med* **384**, 1824-1835 (2021).
19. Ferdinands, J.M. & Shay, D.K. Magnitude of potential biases in a simulated case-control study of the effectiveness of influenza vaccination. *Clin Infect Dis* **54**, 25-32 (2012).
20. Krammer, F. SARS-CoV-2 vaccines in development. *Nature* **586**, 516-527 (2020).
21. Lurie, N.*, et al.* Developing Covid-19 Vaccines at Pandemic Speed. *N Engl J Med* **382**, 1969-1973 (2020).
22. Pardi, N.*, et al.* mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov* **17**, 261-279 (2018).

CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
A. Acetylcholinesterase inhibitor

Myasthenia gravis is caused by the blockage of the postsynaptic receptors, which are activated by acetylcholin (Ach). Acetylcholinesterase is responsible for the hydrolisation of Ach. Thus, acetylcholinesterase inhibitors limit the destruction of Ach, increasing the availability of Ach. This will alleviate the patients' symptoms.

For further reading:
Siegel, A., Sapru, H. Chapter 7: Neurotransmitters in Essential Neuroscience, 4th edition (Wolters Kluwer, Philadelphia, 2019).

During the exam, 28% of the participants answered this question correctly.

Answer question 2:
D. Refer the partner to the urologist

The low amount of proper functioning sperm cells in the semen suggests that there is a male factor involved; something is causing the abnormally low number of sperm cells. Therefore, it is important to firstly establish the reason for this by referring the partner to the urologist.

For further reading:
Smeenk, J., Broer, S. Chapter 13: Infertility in Textbook of Obstetrics and Gynaecology, 1st edition (Bohn Safleu van Loghum, Houten, 2019).

During the exam, 43% of the participants answered this question correctly.

The exam questions can be found back on page 25 in this journal.

WIDE AWAKE WHILE DREAMING
ON LUCID DREAMING AND ITS APPLICATIONS IN THE CLINIC

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Insight

What is something you have always dreamt of doing but never did? Maybe your opportunities lie within your dreams, in your lucid dreams, to be more specific. Lucid dreams are dreams where a person is aware that they are dreaming and, in some cases, is able to influence their dream. A famous lucid dreamer is movie director James Cameron. In an interview, he said that he tried to create a lucid dream in the movie *Avatar* (2009), where the main character is conscious and accesses a different body during his sleep [1]. Even if you do not aspire to be a famous movie director, lucid dreaming might be of interest to you. So, what are lucid dreams, can you learn to become a lucid dreamer, and can lucid dreams be of use for therapeutic purposes?

"Have you ever had a dream, Neo, that you were so sure was real?" This is the question Neo, the protagonist of *The Matrix* (1999), is asked in the first movie [2]. The Matrix is a dream world, and during the movie Neo learns to control this world and beat his enemies. Have you ever had such a dream? A dream where you were aware that you were dreaming or where you were able to influence the course of your dream? If yes, then you might have experienced a lucid dream. Lucid dreaming is a phenomenon where the dreamer is aware of the fact that they are dreaming and might, therefore, be capable of manipulating their dream [3]. About 55% of the population has ever experienced a lucid dream, and about 23% experiences lucid dreams regularly, meaning once a month or more [4]. It sounds exciting to be able to control your dreams, and you might be wondering if you too can learn this. The short answer is yes. At first glance, lucid dreaming seems all fun and games; however, it also has useful applications in the clinic. These clinical applications will be discussed after a concise overview of ways to induce lucid dreaming.

What is lucid dreaming?

Although research about lucid dreaming is a fairly young field in neuroscience, descriptions of the phenomenon have been around for ages, both in Eastern and Western literature. A very early description in Western literature was written by the Greek philosopher Aristotle, who is often seen as the first true scientist. In his text *On Dreams*, he writes: "Often, when one is asleep, there is something in consciousness which declares that what then presents itself is only a dream" [5]. In Eastern cultures, lucid dreaming has a role in various religions, e.g. Buddhism [6]. The term lucid dreaming, however, was not coined until 1913 by the Dutch psychiatrist Frederik van Eeden, who performed research on dreaming [3].

Describing the phenomenon of lucid dreaming is one thing, but proving its existence was a beautiful challenge for neuroscience. The first findings leading to proof of its existence were that lucid dreaming was most likely to occur during rapid eye movement (REM) sleep [7]. During REM sleep, all muscles are paralysed, except for the muscles that control eye movement [8]. Eye movements can be measured using electrooculography [8]. Combining these concepts, researchers came up with the idea that lucid dreamers could, in their sleep, send messages to the researchers using the pre-discussed eye movements. The first scientist who succeeded in this method was Keith Hearne in 1975 [9,10]. However, Stephen LaBerge is often given credit for these findings because he published his findings, while Hearne did not [9,10]. Hearne's participant experienced lucid dreams frequently, and Hearne was able to demonstrate this in the laboratory by using the previously mentioned eye signals [9]. Later research focussed on electrophysiological correlates of lucid dreaming and ways to induce lucid dreaming [10].

Some people talk in their sleep, but what if you could have a conversation with someone experiencing a lucid dream? An intriguing development in the field of lucid dreaming research involved establishing two-way communication between the researcher and the dreamer. In an astounding study by Konkoly *et al.* (2021), four research groups in four different countries managed to establish two-way communication between the researcher and lucid dreamers using several methods [11]. The methods used were solving math problems in morse code (both acoustic and visual), tactile stimulation, spoken math problems, and spoken yes/no questions [12]. Participants in the trial answered with eye movements and gave the correct response in 18% of the experiments, meaning that when two-way communication was established, the answer was correct [11]. In unsuccessful trials, the stimulation was not incorporated in the dreams [12]. Another important finding is that dream reports matched the electrophysiological data. Two-way communication during dreaming can have great potential in enhancing the clinical applications discussed later.

If you were (or maybe are) able to have lucid dreams, what would you do in your dream? Maybe you would do everything the current corona measures forbid, such as meeting with a group of friends or eating out. Maybe you would practice your dance routine one more time because you have a performance tomorrow. Maybe you would try to reorganise your room to make room for a new couch. Research has found that there are several reasons why people engage in lucid dreaming. Using a questionnaire, Stumbrys and Erlacher found that the most common application of lucid dreaming was wish fulfilment (defined as, e.g. flying, dancing, or having sex), followed by solving problems, overcoming fears, spiritual experiences, healing (e.g. for physical pain or handling grief), and training motor skills [13]. They also found that wish fulfilment in particular induced a positive

mood upon awakening, possibly clarifying why it is such a popular application [13]. If these applications have intrigued you, you might be wondering how you can learn to engage in lucid dreaming.

How can I learn it?

In *Inception* (2010), a movie exploring the idea that you can enter someone else's dream without them noticing and implant ideas, one of the main characters explains, "Well, dreams, they feel real while we're in them, right? It's only when we wake up that we realize how things are actually strange" [14]. In order to learn to have lucid dreams, one needs to learn to recognise that they are dreaming, which can be done by learning to recognise the strangeness of a dream. There are several methods to learn to have lucid dreams. We will discuss keeping a dream diary, a reality check with virtual reality, sensory cues, and wake-back-to-bed (WBTB), as these are often used in research. More techniques, that will not be further elaborated, are summarised in the article of Stumbrys *et al.* [15].

If you would ask yourself the question "Is this real?" while you are here reading this article, the answer is probably "Yes". Have you ever asked yourself the same question while dreaming? One of the simplest methods to increase your chances of having a lucid dream is by keeping a dream diary [16]. This will, in the first place, make you more aware of your dreams, and in the second place, allow you to look for recurrent themes in your dreams [16]. If you dream a lot about being on a train, for example, you might ask yourself "Is this real?" while you are actually on the train. You might start to do the same when a train appears in your dream and your dream becomes lucid. If you do not have any recurrent themes in your dreams, you can also do the reality check at random moments during the day, especially in dream-like situations, hoping that you will do the same during dreaming [16]. Researchers have thought of a way to enhance this, as dream-like situations in real life are rather scarce. One of the options they explored is the use of virtual reality to create more dream-like situations [17]. This did increase the tendency of lucid dreaming slightly, but it remained a rare phenomenon [17].

Another technique that is used to increase the rate of lucid dreaming is perceptual cueing. Using this technique, awake participants learn to associate cues with dreaming, the cues being odour, sound, lights, or tactile stimulation [18-20]. These cues are presented while the participant is awake to familiarise the participants with them and associate them with the question: "Am I dreaming?" During REM sleep, the cues are presented again, hoping that they are incorporated into the dream, and the participant becomes lucid [18-20]. Despite the clever idea, success rates remain rather low [18-20].

More promising techniques to increase lucid dreaming are sleep fragmentation and WBTB, often in combination with mnemonic induction of lucid dreaming. With the WBTB technique, participants are woken up during their REM sleep, stay awake for a certain amount of time, and go back to sleep after [21]. During the time awake, mnemonic induction of lucid dreaming is used. This is a technique where participants practice recalling their dreams, recognising dream-like features, and telling themselves that they will notice that they are dreaming the next time [21]. This increases the chances of lucid dreaming [21]. Sleep fragmentation refers to the phenomenon of alternated sleep-wake cycles [22]. Both of these methods reported increased lucid dreaming frequency in participants [21,22]. Concluding, there are several methods to induce or increase lucid dreaming, with different success rates. However, no magic bullet has been found yet.

Dream your fears away

While we mentioned earlier that wish fulfilment is the most used application of lucid dreaming, there has been growing interest in using lucid dreaming as a treatment approach for several psychiatric disorders. Perhaps the most obvious clinical application of lucid dreaming would be to overcome recurrent nightmares. Recurrent nightmares often occur in the context of post-traumatic stress disorder but can also present themselves without trauma, as well as in other psychiatric disorders, such as depression and anxiety [23]. Nightmares decrease sleep quality, may cause fear to fall asleep, and decrease daily functioning and quality of life during daytime [23]. Lucid dreaming as a therapy aims to make the patient aware of the fact that they are dreaming, enabling the patient to change the course of their nightmare. For example, if a nightmare is about being chased, a common nightmare theme, the dreamer can change or stop the chasing if the dream becomes lucid chasing [24]. They could, for instance, decide to stop running, turn around, and change their chaser into Elsa from *Frozen* singing *Let It Go* [25]. In this case, lucid dreaming helps against your fear by making it preposterous, similar to the Riddikulus spell in *Harry Potter*. This spell turns a Boggart, embodying your greatest fear, into something ridiculous, just like in the *Frozen* example [26]. However, the exact efficacy is not known yet [27]. A recent review by De Macêndo *et al.* concludes that lucid dreaming therapy has the potential to help people suffering from nightmares, but these results are still inconsistent [27]. One of the main limitations is that, so far, not all participants become able to have lucid dreams [27].

Similar to defeating nightmares, people with anxiety or phobias could use the lucid dreaming environment to tackle their fears. Simulation is often mentioned as one of the functions of dreaming, as dreams would be a safe environment to practice new behaviour [28]. In this way, lucid dreaming could be used as an add-on or enhancement to current exposure therapies. However, no such studies have been performed yet.

One study investigated the relationship between depression and lucid dreaming [29]. The hypothesis was that a higher lucid dreaming frequency would be associated with lower depression scores, mediated by the locus of control (LOC) [28]. The LOC is a concept that refers to whether you are in control of your life (internal LOC) or that external forces control your life (external LOC) [30]. A strong external LOC is associated with depression, while lucid dreaming is associated with a higher internal LOC [31,32]. Moreover, lucid dreaming is associated with a better mood [13]. Disappointingly, lucid dreaming frequency correlated positively with depression scores [29]. The author discusses that it is not yet clear in which direction causation goes, and more research is needed to investigate the relation between lucid dreaming and depression [29]. Concluding, lucid dreaming as a therapy has mostly been explored for recurrent nightmares, both idiopathic and in several psychiatric disorders. We are just at the dawn of lucid dreaming research, so more clinical applications might be around the corner.

Conclusion

James Cameron uses his dreams as inspiration for movies, but we now know that lucid dreaming can also offer us other purposes. Lucid dreaming is a phenomenon where the dreamer is aware that they are dreaming. Lucid dreaming can be induced via several methods, such as keeping a dream diary, virtual reality, sensory cueing, and using the WBTB method. Not all methods have similar success rates, and there is no method yet that can teach everyone to become lucid, nor a method to make people have lucid dreams every night. Lucid dreaming can be used to treat recurrent nightmares by

allowing people to have control over the storyline of their nightmare. For now, the biggest issue in lucid dreaming therapy research is that not yet everyone is able to learn to have lucid dreams. In addition, lucid dreaming research shows very mixed results. Maybe in the future, lucid dreaming might offer us possibilities where researchers now only dream about.

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References

1. Hollinger, A. (2010, 20 April). Cameron with Lucid Dreams as Avatar Blu-ray Bows on Earth Day 4/22. Hollywood Today. https://web.archive.org/web/20140906214624/http://www.hollywoodtoday.net/2010/04/20/cameron-with-lucid-dreams-as-avatar-blu-ray-bows-on-earth-day-422/
2. Wachowski, L., & Wachowski, L. (1999). The Matrix. Warner Bros.
3. Van Eeden, F. A study of dreams. in Proceedings of the society for psychical research, Vol. **26** 431-461 (1913)
4. Saunders, D.T., et al. Lucid dreaming incidence: A quality effects meta-analysis of 50years of research. Consciousness and Cognition **43**, 197-215 (2016).
5. Aristotle, On Dreams
6. Gillespie, G. Lucid dreams in Tibetan Buddhism. in Conscious mind, sleeping brain, Vol. **27-35** (Springer, 1988).
7. Green, C. Lucid dreams, (Institute of Psychophysical Research, Oxford, 1968).
8. Siegel, J.M. REM sleep. Principles and practice of sleep medicine **4**, 120-135 (2005)
9. Hearne, K.M.T. (1977). Eye-movement communication from lucid dreams: A new technique and initial findings. Paper given to 11th Post-doctoral Conference in the Behavioural Sciences, Hull University, April 15-18
10. Dresler, M., et al. Neural correlates of dream lucidity obtained from contrasting lucid versus non-lucid REM sleep: a combined EEG/fMRI case study. Sleep **35**, 1017-1020 (2012)
11. La Berge, S.P., et al. Lucid dreaming verified by volitional communication during REM sleep. Percept Mot Skills **52**, 727-732 (1981).
12. Konkoly, K.R., et al. Real-time dialogue between experimenters and dreamers during REM sleep. Current Biology **12**, 1417-1427 (2021)
13. Stumbrys, T. & Erlacher, D. Applications of lucid dreams and their effects on the mood upon awakening. International Journal of Dream Research **9**, 146-150 (2016).
14. Nolan, C. 2010. Inception. United States: Warner Bros.
15. Stumbrys, T., et al. Induction of lucid dreams: a systematic review of evidence. Conscious Cogn **21**, 1456-1475 (2012).
16. Tholey, P. Techniques for Inducing and Manipulating Lucid Dreams. Perceptual and Motor Skills **57**, 79-90 (1983)
17. Gott, J., et al. Virtual reality training of lucid dreaming. Philos Trans R Soc Lond B Biol Sci **376**, 20190697-20190697 (2021)
18. Erlacher, D., et al. Inducing lucid dreams by olfactory-cued reactivation of reality testing during early-morning sleep: A proof of concept. Consciousness and Cognition **83**, 102975 (2020).
19. Laberge, S. & Levitan, L. Validity established of DreamLight cues for eliciting lucid dreaming. Dreaming **5**, 159 (1995).
20. Paul, F., et al. Lucid dream induction by visual and tactile stimulation: An exploratory sleep laboratory study. International Journal of dream research **7**, 61-66 (2014).
21. Erlacher, D. & Stumbrys, T. Wake Up, Work on Dreams, Back to Bed and Lucid Dream: A Sleep Laboratory Study. Front Psychol **11**, 1383-1383 (2020).
22. Gott, J., et al. Sleep fragmentation and lucid dreaming. Consciousness and Cognition **84**, 102988 (2020)
23. Gieselmann, A., et al. Aetiology and treatment of nightmare disorder: State of the art and future perspectives. J Sleep Res **28**, e12820-e12820 (2019)
24. Schredl, M. Nightmare frequency and nightmare topics in a representative German sample. European Archives of Psychiatry and Clinical Neuroscience **260**, 565-570 (2010)
25. Buck, C., & Lee, J. (2013). Frozen. Walt Disney Studios Motion Pictures.
26. Rowling, J.K.A. Harry Potter and the prisoner of Azkaban, (First edition. New York : Arthur A. Levine Books, 1999)
27. De Macêdo, T.C.F., et al. My Dream, My Rules: Can Lucid Dreaming Treat Nightmares? Front Psychol **10**, 2618-2618 (2019).
28. Revonsuo, A. & Valli, K. Dreaming and consciousness: Testing the threat simulation theory of the function of dreaming. Psyche: An Interdisciplinary Journal of Research on Consciousness (2000)
29. Taitz, I. Learning lucid dreaming and its effect on depression in undergraduates. (2011)
30. Rotter, J.B. Generalized expectancies for internal versus external control of reinforcement. Psychol Monogr **80**, 1-28 (1966)
31. Presson, P.K. & Benassi, V.A. Locus of control orientation and depressive symptomatology: A meta-analysis. Journal of Social Behavior and Personality **11**, 201 (1996)
32. Blagrove, M. & Hartnell, S.J. Lucid dreaming: associations with internal locus of control, need for cognition and creativity. Personality and Individual Differences **28**, 41-47 (2000)

THE IMPACT OF MYOTONIC DYSTROPHY ON THE BRAIN AND SLEEP

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Review

Abstract

Myotonic dystrophy type 1 is a multisystemic neurological disorder with a CTG trinucleotide repeat expansion in the 3'UTR of the *DMPK* gene. One of the manifestations with a severe impact on daily life is the dysfunction of the central nervous system (CNS), such as excessive daytime sleepiness (EDS), which can lead to cognitive problems. In this review, we try to gain more profound knowledge on the cause of the cognitive impairment in individuals with myotonic dystrophy type 1 and its relationship with EDS. Previous research has shown that individuals with this disorder have atrophy in both white and grey matter, contributing to a decrease in the volume of the brain. These changes in brain structure seem to influence EDS. As it has been shown that sequestering of muscleblind-like proteins affects splicing, it is thought that changes in downstream proteins might be the cause of the CNS defects. Brain structures that are mainly affected in EDS are the brainstem regions involved in the sleep-wake cycle. Next to this, a correlation has been found between atrophy of the corpus callosum and EDS. These disturbances could lead to alteration of the sleep-wake system and rapid eye movement sleep dysregulation. Thus, evidence suggests that the proposed mechanism causing EDS is related to primary disturbances in CNS.

KEYWORDS: Myotonic dystrophy, excessive daytime sleepiness, CNS

Myotonic dystrophy type 1 (DM1) is a dominant, autosomal inherited disease caused by a progressive cytosine-thymine-guanine (CTG) trinucleotide repeat expansion in the 3' untranslated region (UTR) of the *DMPK* gene, located on chromosome 19q13.3 [1]. The *DMPK* gene codes for myotonic dystrophy protein kinase (DMPK), which is expressed in muscle, heart, and brain cells, among other tissue types [1]. DM1 is, therefore, classified as a multisystemic neurological disease. It is the most common muscular disorder, with an estimated prevalence of 1:8,000 [1]. The clinical manifestations are widely variable and include dysfunctions in the central nervous system (CNS), such as hypersomnia, apathy, visuospatial abnormalities, working memory deficits, and excessive daytime sleepiness (EDS) [1-3]. Next to these, symptoms include muscle atrophy and myotonia, cataracts, gastrointestinal manifestations, cardiac abnormalities, and endocrine system-related manifestations, such as diabetes, thyroid dysfunction, and hypogonadism (Figure 1).

Due to the enormous negative impact on the lives of individuals with DM1, dysfunction of the CNS has become of considerable interest within the field of medical research. Recent studies provided initial experimental evidence that several brain areas are affected and suggested damaged proteins causing neuronal defects [4, 5]. Several cognitive dysfunctions have been associated with DM1, including defects in the memory of the patients. However, a condition that also severely affects the lifestyle of individuals with DM1 is EDS [6]. This dysfunction is present in up to 80% of the patients, and effective treatment is not yet available [7]. Sleep-related disordered breathing in individuals with DM1 has previously been thought to be associated with EDS. However, it has been shown that even if the sleep-related disordered breathing is treated well, the EDS persists and must, thus, have a different underlying mechanism. Therefore, researchers started an investigation at a structural and molecular level in the brain as the underlying cause(s) for the EDS could possibly be located there [7].

Patients with EDS have a high desire to sleep, which is only slightly improved through sleeping [6]. Their sleepiness, however, increases with rest, and patients tend to take daytime naps easily. Yet, these naps seem to be unrefreshing without associated dream content [6]. Additionally, the quality of life is decreased through the with EDS-occurring low energy, further contributing to a decrease in memory, concentration, and motivation [6]. Patients have difficulty staying awake after meals and might fall asleep at work [7]. EDS has a high impact on the quality of life of individuals with DM1; thus, a deeper insight into the mechanism is to improve the life of patients.

Therefore, in this article, we will review existing literature to gain in-depth knowledge on the causes of cognitive impairment in DM1

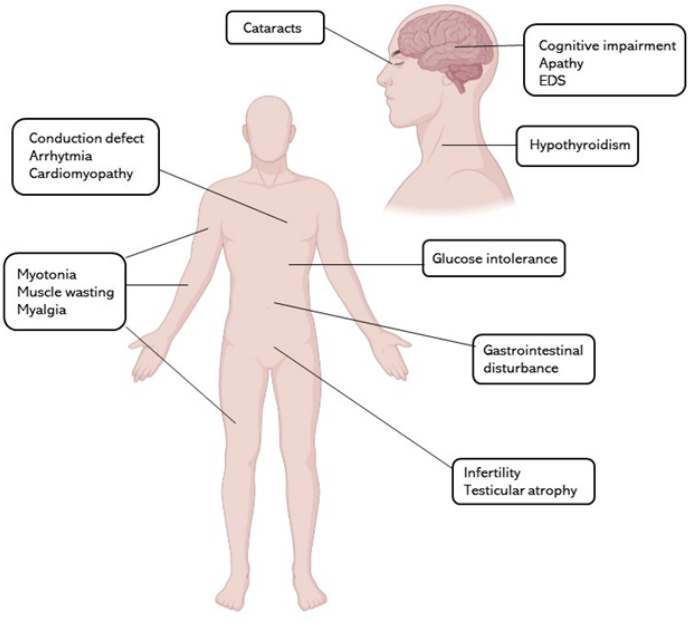

Figure 1: *Symptoms related to myotonic dystrophy type 1 (Takeda, S. et al., 2016). EDS = excessive daytime sleepiness*

and its relationship with excessive daytime sleepiness. This will hopefully lead to a better understanding of this area in the disease.

Pathophysiology

As previously mentioned, the CTG repeat is expanded in DM1 patients [1]. Healthy individuals have between 5-37 CTG triplets in the *DMPK* gene, whereas DM1-affected individuals carry repeat expansions with a length of 50 to over 1,000s of CTG triplets [8]. The length of this expansion correlates with the severity of the disease and the earlier onset of symptoms in life. However, this correlation is not proven for the severity of EDS [9]. In individuals with a repeat number above 38, the repeat can undergo a somatic expansion, which is the largest in brain and muscle cells but also takes place in the germline cells, where it leads to genetic anticipation. In other cells in the body, like the blood cells, the CTG expansion accumulates at a lower rate, suggesting that the expansion rate is tissue-specific [10]. This expansion over a patient's lifetime leads to the increase of severity of most features of the disease [11]. The main mechanism thought to be responsible for the somatic expansion takes place during DNA repair [12]. The long repeat expansions can form hairpin structures that are recognised by DNA polymerase II during replication. A random hairpin formation can also lead to the recruitment of the mismatch repair proteins MSH2 and MSH3 [12]. These proteins cut the DNA strand at the loops. If the strands then slip, gaps are formed that are subsequently filled with more repeats, causing the increased number of CTG triplets [12].

Molecular mechanisms

In the brain, there are several ways in which the elongated repeat can affect the protein its function. The primary mechanism underlying the dysfunction of several proteins is thought to be caused by the in hairpin folded RNA repeat that cannot leave the nucleus [3]. These formed foci then bind other essential RNA-binding proteins needed for splicing and/or transcription [3]. These proteins can, therefore, not execute their function anymore, leading to defective proteins [3].

The RNA binding protein muscleblind-like (MBNL) 2 is sequestered by the repeat expansion, leading to a loss of function of this protein. The loss of MBNL2 leads to a change in alternative polyadenylation regulation [13]. It also affects the splicing of other proteins, which is thought to cause the CNS defects, including changes in rapid eye movement (REM) sleep [14]. Proteins that are affected by the missing splicing proteins include tau, NMDA receptor 1, and the amyloid precursor protein [15, 16]. Tau is responsible for the stabilisation of microtubules, and, if defected, it can form neurofibrillary tangles instead, which are aggregates of hyperphosphorylated tau [15]. Aggregates are found in the limbic system, brainstem, hippocampus, entorhinal cortex, and temporal cortical areas of DM1 patients [17]. NMDA receptor 1 is needed for long-term potentiation in the hippocampus [16].

Changes in the brain structure

Imaging studies have shown pathological abnormalities of the CNS in DM1 patients [18-37]. Among others, the calculated brain parenchymal fraction showed that there was global brain atrophy in DM1 patients (Figure 2) [20, 21, 38]. In adult DM1, brain atrophy progresses with age, whereas in juvenile DM1, atrophy is present in early childhood [39]. Additionally, some studies have shown a dilatation of the Virchow-robin spaces (extensions of the subarachnoid space) [20, 22, 23]. This dilatation is mainly shown in young DM1 patients [24]. On top of that, voxel-based morphometry and MRI studies found a decrease in the grey matter volume in all cortical lobes, the basal ganglia, and the cerebellum [5, 39, 40].

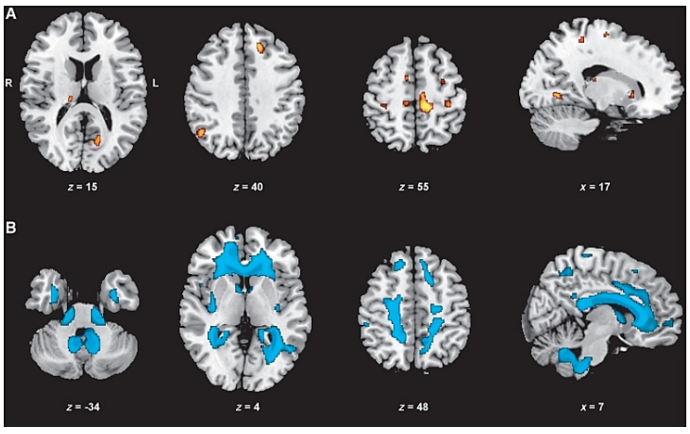

Figure 2: *The neuroimaging of the brain of DM1 patients with VBM. The top row displays areas of gray matter decrease in DM1 patients compared with controls. The bottom row displays areas of white matter decrease in DM1 patients compared with controls (Minnerop et al., 2011).*

However, damage to the white matter tract was much more dominant than the effect of DM1 on the grey matter tract [5]. In these MRI and voxel-based morphometry studies, white matter hyperintensities were mainly found at the level of the frontal and temporal lobe [5, 38-40]. Caso *et al*. found that white matter hyperintensities were associated with memory, executive, reasoning, and visuospatial impairments [22]. Several studies also suggest that the extent of the white matter intensities is related to cognitive deficits in DM1 patients [26, 28-30, 41, 42]. However, other studies do not confirm this relationship [33, 43, 44].

The damage of these white matter tracts affects the association fibres (axons that connect regions within one hemisphere), the commissural fibres (axons that connect the hemispheres), mainly the corpus callosum, and the projection fibres in the brainstem (in both in- and external capsules) [5, 33, 37]. Brain atrophy and white matter involvement will progress over time in DM1 patients [45]. Furthermore, the strength and the local efficiency of the white matter networks is lower in DM1 patients compared to unaffected controls, although the number of connections is not aberrant [36]. A proposed mechanism by Dorst *et al.* regarding CNS symptoms is that they are associated with these above described structural alterations in the white matter network [36]. With transcranial sonography, studies can measure the echogenicity of the brainstem raphe, mesencephalon, substantia nigra, and third ventricle [5]. A hypoechogenicity of the brainstem raphe was seen in DM1 patients. This hypoechogenicity was also significantly associated with excessive daytime sleepiness in DM patients [35]. Most studies show no correlation between the neuropathological changes and the length of the CTG repeat [5].

Effects of DM1 on EDS

Some studies have been performed to investigate the cause of EDS [20, 46-50]. However, its pathogenicity still remains unclear. As a consequence, research began to focus on the different processes that are involved in primary CNS disturbances in DM1 [5]. It is hypothesised that these disturbances could lead to alterations of the sleep-wake system and REM sleep dysregulation [5].

MRI studies were conducted to investigate these disturbances. Cabada *et al.* showed an association between EDS and a decrease of the volume in the right ventral diencephalon and right pallidum [20]. Additionally, damage to the brainstem regions that control sleep was found to be a possible cause of EDS [39]. A correlation between EDS and corpus callosum atrophy has also been seen [46].

However, how these changes in brain structure cause and influence EDS is still unclear. Besides changes in the brain structure, some other mechanisms have been proposed to be involved in the primary CNS disturbances related to DM1 [6, 7]. A disruption of the pulsatile secretion of cortisol and growth hormone and increased cytokine levels were found to be involved in EDS [49, 50].

On the more molecular level, a defect in the synthesis of the neuropeptide Orexin-A/Hypocretin-1 is known to be involved in narcolepsy, which symptoms also include EDS. Therefore, it was investigated if this might also be a cause for EDS in DM1 patients [47]. A significantly lower level of Hypocretin-1 in DM1 patients was found compared to idiopathic hypersomnia patients that are considered normal Hypocretin-1 levels in the cerebrospinal fluid ($p<0.001$) [47]. However, a more recent study could no longer show this significant difference ($p<0.001$), meaning that Hypocretin-1 might influence EDS in patients but that it is not the primary cause [48].

Solutions for EDS in DM1 patients have not yet been found. Besides the treatment for muscle-related causes of sleepiness, which include breathing difficulty, there are only a few medications that treat other possible causes for the EDS. Modafinil is used to treat excessive somnolence in DM1 patients [51, 52]. The exact mechanism of Modafinil is not clear yet but is thought to act through various neurotransmitters, especially in the hypothalamus [53]. Apart from Modafinil, there seem to be no major treatment methods for EDS.

Conclusion

Based on the available literature summarised in this article, we found that in DM1 a multitude of brain areas are affected and show atrophy [5, 20, 23, 24, 35, 38-40]. The cause of this atrophy is not clear, but on the molecular level, sequestering of MBNL by the elongated repeat could be one of its causes [13]. For EDS in individuals with DM1, the proposed mechanisms are related to primary disturbances in the CNS, especially in the brainstem [5]. It is suggested that these could lead to modification of the sleep-wake systems and REM sleep dysregulation [6, 7]. Further research needs to be done on the brain-related cause of EDS in DM1 patients to gain a more profound knowledge of the potential mechanism. This could enhance adequate patient management regarding DM1 and EDS, lead to better treatment possibilities, and improve the patients' quality of life.

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References

1. Meola, G. & Cardani, R. Myotonic dystrophies: An update on clinical aspects, genetic, pathology, and molecular pathomechanisms. *Biochimica et biophysica acta* **1852**, 594-606 (2015).
2. Pelargonio, G., *et al.* Myotonic dystrophy and the heart. *Heart (British Cardiac Society)* **88**, 665-670 (2002).
3. De León, M.B. & Cisneros, B. Myotonic dystrophy 1 in the nervous system: from the clinic to molecular mechanisms. *Journal of neuroscience research* **86**, 18-26 (2008).
4. Lee, K.-Y., *et al.* Deprivation of Muscleblind-Like Proteins Causes Deficits in Cortical Neuron Distribution and Morphological Changes in Dendritic Spines and Postsynaptic Densities. *Frontiers in Neuroanatomy* **13**(2019).
5. Minnerop, M., *et al.* Current Progress in CNS Imaging of Myotonic Dystrophy. *Front Neurol* **9**, 646-646 (2018).
6. Laberge, L., *et al.* Daytime sleepiness and myotonic dystrophy. *Current neurology and neuroscience reports* **13**, 340 (2013).
7. Dauvilliers, Y.A. & Laberge, L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. *Sleep medicine reviews* **16**, 539-545 (2012).
8. Souidi, A., *et al.* Dissecting Pathogenetic Mechanisms and Therapeutic Strategies in Drosophila Models of Myotonic Dystrophy Type 1. *Int J Mol Sci* **19**, 4104 (2018).
9. Laberge, L., *et al.* Sleep complaints in patients with myotonic dystrophy. *Journal of sleep research* **13**, 95-100 (2004).
10. Thornton, C.A., *et al.* Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than in leukocytes. *Ann Neurol* **35**, 104-107 (1994).
11. Yum, K., *et al.* Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. *Curr Opin Genet Dev* **44**, 30-37 (2017).
12. Mcmurray, C.T. Mechanisms of trinucleotide repeat instability during human development. *Nature reviews. Genetics* **11**, 786-799 (2010).
13. Goodwin, M., *et al.* MBNL Sequestration by Toxic RNAs and RNA Misprocessing in the Myotonic Dystrophy Brain. *Cell Rep* **12**, 1159-1168 (2015).
14. Charizanis, K., *et al.* Muscleblind-like 2-mediated alternative splicing in the developing brain and dysregulation in myotonic dystrophy. *Neuron* **75**, 437-450 (2012).
15. Wang, Y., *et al.* Tau exons 2 and 10, which are misregulated in neurodegenerative diseases, are partly regulated by silencers which bind a SRp30c.SRp55 complex that either recruits or antagonizes htra2beta1. *The Journal of biological chemistry* **280**, 14230-14239 (2005).
16. Jiang, H., *et al.* Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscleblind proteins and deregulated alternative splicing in neurons. *Human molecular genetics* **13**, 3079-3088 (2004).
17. Itoh, K., *et al.* Neuropathology does not Correlate with Regional Differences in the Extent of Expansion of CTG Repeats in the Brain with Myotonic Dystrophy Type 1. *Acta Histochem Cytochem* **43**, 149-156 (2010).
18. Baldanzi, S., *et al.* Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1. *Neuroimage Clin* **12**, 190-197 (2016).
19. Minnerop, M., *et al.* Current Progress in CNS Imaging of Myotonic Dystrophy. *Front Neurol* **9**, 646 (2018).
20. Cabada, T., *et al.* Brain Involvement in Myotonic Dystrophy Type 1: A Morphometric and Diffusion Tensor Imaging Study with Neuropsychological Correlation. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* **32**, 401-412 (2017).
21. Kassubek, J., *et al.* Quantification of brain atrophy in patients with myotonic dystrophy and proximal myotonic myopathy: a controlled 3-dimensional magnetic resonance imaging study. *Neurosci Lett* **348**, 73-76 (2003).
22. Caso, F., *et al.* Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. *PLoS One* **9**, e104697 (2014).
23. Di Costanzo, A., *et al.* Dilated Virchow-Robin spaces in myotonic dystrophy: frequency, extent and significance. *Eur Neurol* **46**, 131-139 (2001).
24. Schneider-Gold, C., *et al.* Cortical and Subcortical Grey and White Matter Atrophy in Myotonic Dystrophies Type 1 and 2 Is Associated with Cognitive Impairment, Depression and Daytime Sleepiness. *PLoS One* **10**, e0130352 (2015).

25. Abe, K., *et al.* Involvement of the central nervous system in myotonic dystrophy. *J Neurol Sci* **127**, 179-185 (1994).
26. Bachmann, G., *et al.* The clinical and genetic correlates of MRI findings in myotonic dystrophy. *Neuroradiology* **38**, 629-635 (1996).
27. Huber, S.J., *et al.* Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy. *Arch Neurol* **46**, 536-540 (1989).
28. Kuo, H.C., *et al.* Correlation among subcortical white matter lesions, intelligence and CTG repeat expansion in classic myotonic dystrophy type 1. *Acta neurologica Scandinavica* **117**, 101-107 (2008).
29. Romeo, V., *et al.* Brain involvement in myotonic dystrophies: neuroimaging and neuropsychological comparative study in DM1 and DM2. *Journal of neurology* **257**, 1246-1255 (2010).
30. Weber, Y.G., *et al.* Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2. *Neurology* **74**, 1108-1117 (2010).
31. Ota, M., *et al.* Relationship between diffusion tensor imaging and brain morphology in patients with myotonic dystrophy. *Neurosci Lett* **407**, 234-239 (2006).
32. Di Costanzo, A., *et al.* Brain MRI features of congenital- and adult-form myotonic dystrophy type 1: case-control study. *Neuromuscul Disord* **12**, 476-483 (2002).
33. Fukuda, H., *et al.* Diffusion tensor imaging of cerebral white matter in patients with myotonic dystrophy. *Acta radiologica (Stockholm, Sweden : 1987)* **46**, 104-109 (2005).
34. Conforti, R., *et al.* Brain MRI abnormalities in the adult form of myotonic dystrophy type 1: A longitudinal case series study. *Neuroradiol J* **29**, 36-45 (2016).
35. Krogias, C., *et al.* Evaluation of CNS involvement in myotonic dystrophy type 1 and type 2 by transcranial sonography. *Journal of neurology* **262**, 365-374 (2015).
36. Van Dorst, M., *et al.* Structural white matter networks in myotonic dystrophy type 1. *Neuroimage Clin* **21**, 101615 (2019).
37. Minnerop, M., *et al.* The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease. *Brain* **134**, 3530-3546 (2011).
38. Baldanzi, S., *et al.* Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1. *NeuroImage: Clinical* **12**, 190-197 (2016).
39. Caso, F., *et al.* Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. *PLoS One* **9**, e104697-e104697 (2014).
40. Okkersen, K., *et al.* Brain imaging in myotonic dystrophy type 1: A systematic review. *Neurology* **89**, 960-969 (2017).
41. Abe, K., *et al.* Involvement of the central nervous system in myotonic dystrophy. *Journal of the neurological sciences* **127**, 179-185 (1994).
42. Huber, S.J., *et al.* Magnetic Resonance Imaging and Clinical Correlates of Intellectual Impairment in Myotonic Dystrophy. *Archives of Neurology* **46**, 536-540 (1989).
43. Ota, M., *et al.* Relationship between diffusion tensor imaging and brain morphology in patients with myotonic dystrophy. *Neurosci Lett* **407**, 234-239 (2006).
44. Di Costanzo, A., *et al.* Brain MRI features of congenital- and adult-form myotonic dystrophy type 1: case-control study. *Neuromuscular disorders : NMD* **12**, 476-483 (2002).
45. Conforti, R., *et al.* Brain MRI abnormalities in the adult form of myotonic dystrophy type 1: A longitudinal case series study. *Neuroradiol J* **29**, 36-45 (2016).
46. Giubilei, F., *et al.* Excessive daytime sleepiness in myotonic dystrophy. *Journal of the neurological sciences* **164**, 60-63 (1999).
47. Martínez-Rodríguez, J.E., *et al.* Decreased hypocretin-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. *Sleep* **26**, 287-290 (2003).
48. Omori, Y., *et al.* Orexin/hypocretin levels in the cerebrospinal fluid and characteristics of patients with myotonic dystrophy type 1 with excessive daytime sleepiness. *Neuropsychiatric disease and treatment* **14**, 451-457 (2018).
49. Johansson, A., *et al.* Abnormal cytokine and adrenocortical hormone regulation in myotonic dystrophy. *J Clin Endocrinol Metab* **85**, 3169-3176 (2000).
50. Culebras, A., *et al.* Absence of sleep-related growth hormone elevations in myotonic dystrophy. *Neurology* **27**, 165-167 (1977).
51. Macdonald, J.R., *et al.* Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy. *Neurology* **59**, 1876-1880 (2002).
52. Talbot, K., *et al.* Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy. *Neuromuscular disorders : NMD* **13**, 357-364 (2003).
53. Easow Mathew, M., *et al.* Modafinil for excessive daytime sleepiness. *Cochrane Database Syst Rev* **2017**, CD010843 (2017).

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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Harshitha Ramu[1]

Summary

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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Real-time communication while dreaming – a reality?

We are transported to alternate realities when we dream. These surreal experiences constitute a major part of human sleep, but they are yet to be fully understood. Neuroscientific studies about dreams are challenging due to the fact that reporting of dreams in a retrospective manner is often warped, caused by forgetfulness and distorted memories. This very challenge drove researchers Gott *et al.* (Donders Institute for Brain, Cognition and Behaviour, Radboudumc) in collaboration with researchers around the world to investigate whether there is a way to communicate with dreamers in real-time in order to allow the empirical exploration of dreams. In their recent publication in *Current Biology,* published by *Cell Press* (impact factor = 9.6 and 38.6, respectively), they showed that participants who were capable of lucid dreaming, a type of dream wherein the subject is aware that they are dreaming, were able to comprehend questions asked by an experimenter. Further, it also demonstrated that dreamers were able to answer the questions using certain electrophysiological signals. After rapid-eye-movement sleep was verified using polysomnography in 36 participants, procedures for two-way communication were implemented between the experimenters and the test subjects. The results documented the ability of six participants to correctly answer asked questions such as math problems and their ability to perceive novel information such as tactile stimuli, which occurred on 29 different occasions. Output signals recorded to ascertain the accuracy of the answers included distinctive eye movements and facial muscle contractions. These results obtained independently across four laboratories provide evidence of the possibility to empirically explore the conscious and cognitive attributes of dreaming in real-time. This study opens up a new platform for the exploration of the mystical world of dreams and for the development of new practical applications to promote better sleep and well-being [2].

What is the role of neutrophils in psoriasis?

Psoriasis can be defined as a chronic inflammatory autoimmune disease that primarily affects the skin but is also detrimental to other tissues and organs. Although the accumulation of neutrophils in psoriatic skin is recognised as a hallmark of the disease, their role in aiding the progression of inflammation is not established. Recent novel insights about the phenotype and functional heterogeneity of neutrophils in other chronic inflammatory diseases such as rheumatoid arthritis drove Rodriguez-Rosales *et al.* (Department of Laboratory Medicine, Radboudumc) to explore the same in the context of psoriasis. In this observational study published in *The Journal of Allergy and Clinical Immunology* (impact factor = 14.1), 32 psoriasis patients were included across two university hospitals. Patient-derived blood and skin samples were collected, and neutrophil phenotype and functions were investigated using flow cytometry, multispectral imaging, multiplex immunohistochemistry, and *in vitro* co-culture stimulation assays. The results revealed a unique composition of neutrophils and the increased presence of two distinct subtypes of neutrophils, i.e. $CD10^{pos}$ (p=0.00008) and $CD10^{neg}$ (p=0.008), in the blood. Further, it was shown that a subset of aged $CD10^{neg}$ neutrophils was three times more abundant in the patients compared to healthy individuals. These aged neutrophils exhibited abnormal neutrophil functions and mediated the production of pro-inflammatory cytokines, such as IL-17 and IFN-γ, by T-cells, *in vitro* via the formation of neutrophil extracellular traps. Upon multiplex immunohistochemistry of psoriatic skin lesions from six patients, the presence of aged neutrophils in the proximity of T-cells was documented. Finally, targeted biological therapy using TNF-α and p40 (IL-12/IL-23) antibody therapy decreased the number of aged neutrophils in circulation, leaving the number of mature neutrophils unaffected. This study provides evidence about the pro-inflammatory role of certain subtypes of neutrophils in psoriasis and sheds light on their prognostic and therapeutic value [3].

Urbanisation is associated with an inflammatory status

Sub-Saharan Africa is currently undergoing a notable rural-to-urban transition, which has implications for the increased occurrence of non-communicable diseases. Important changes occurring during this wave of urbanisation include alterations in diet and physical activity, commonly termed as a "nutritional transition". Previous studies have underlined the impact of bacterial metabolites and diet on inflammation and immunity. Through this study, Temba *et al.* (Department of Internal Medicine, Radboudumc), in collaboration with Kilimanjaro Christian Medical University College, University of Bonn, and University of Groningen, aimed to elucidate the interaction of metabolic and immune consequences of urbanisation with demographic, dietary, and environmental factors in a cohort of 323 healthy Tanzanians. The effects of rural-urban dwelling on the immune cell transcriptome, plasma metabolome, inflammation, and host defence were studied using whole blood samples and published in *Nature Immunology* (impact factor = 20.48). The results showed that the transcriptional signature of urban dwellers varied from their rural counterparts, greatly characterised by an interferon-signalling program. Further, it was demonstrated that urban Tanzanians produced more pro-inflammatory cytokines (p<0.001). The underlying differences in endogenous and food-derived metabolites, which are possibly causative for alterations in cytokine profiles, were also identified among urban and rural dwellers. Another interesting observation was that the serum obtained from urban dwellers induced functional reprogramming of innate immune cells, making them into a pro-inflammatory phenotype with higher TNF production (p< 0.001). It was shown that apigenin, a flavone (a compound in plants) abundantly found in the plasma of rural dwellers (p<0.0001), can inhibit the induction of this pro-inflammatory functional reprogramming. This finding highlighted the importance of the anti-inflammatory, rich in flavonoids, traditional plant-based diets in modulating disease epidemiology in Sub-Saharan Africa and other populations. Together, these findings present novel insights as to how urbanisation and nutritional transition affect the rate of onset of inflammatory diseases and how well-regulated use of natural resources can improve the overall health of populations [4].

References

1. Radboudumc. "Onze impact in 2020" *Impact 2020* (2020). https://www.radboudumc.nl/over-het-radboudumc/impact-2020
2. Konkoly, K.R., *et al.* Real-time dialogue between experimenters and dreamers during REM sleep. *Curr Biol* **12**, 1417-1427 (2021).
3. Rodriguez-Rosales, Y.A., *et al.* Immunomodulatory aged neutrophils are augmented in blood and skin of psoriasis patients. *J Allergy Clin Immunol* (2021).
4. Temba, G.S., *et al.* Urban living in healthy Tanzanians is associated with an inflammatory status driven by dietary and metabolic changes. *Nat Immunol* **22**, 287-300 (2021).

RAMS

A Word from the Board of RAMS

Dear reader,

Thank you for reading the nineteenth edition of RAMS. We hope that you enjoyed this insight into (bio)medical research. I would like to thank the editorial board, editors, reviewers, and all other people involved for their contribution to this edition.

As I sat down to write this, I realised that time flies. The nineteenth edition is already the fourth release of RAMS in this academic year. This means we are close to the end of the academic year, meaning that my board year is about to end. I have learned a lot from RAMS during the past months, and I hope you did too! Despite the pandemic and its related restrictions, I am proud of what we have achieved. Together, we succeeded in organising engaging online symposia, masterclasses, and RAMS research rounds, and all of us connected and learned from each other virtually.

My board year may almost come to an end, but I can assure you that I will always stay connected with RAMS. RAMS has become part of me, and I hope it will become part of you as well. Our mission is to motivate you to dig deeper into the fascinating world of scientific research. I hope this edition enthused you to do so.

Stay curious and take care.

On behalf of the board of RAMS,

Hajar Rotbi
Treasurer of RAMS 2020-2021

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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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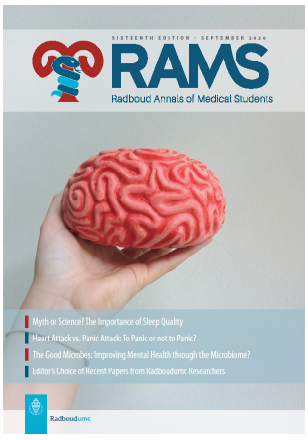

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