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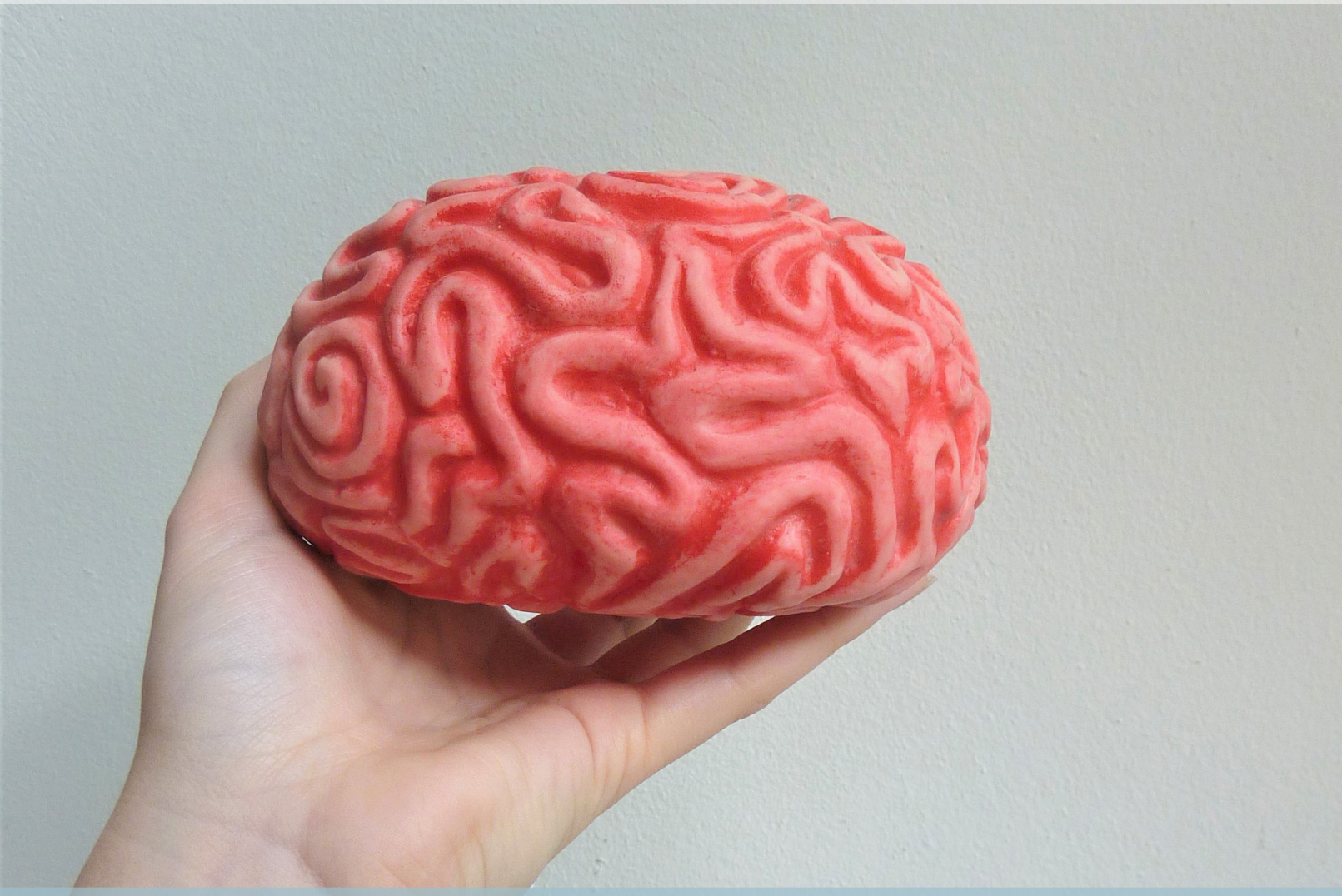

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FROM THE EDITORIAL BOARD

Dear reader,

It is my pleasure to present to you the 16th edition of RAMS which also marks the end of our time as members of the editorial board. As this semester is coming to an end, we would like to thank you for once again picking up this brand-new RAMS edition!

Looking back on a year full of surprises and challenges, we learnt valuable things and made long-lasting memories. It was a truly remarkable time to be the chair of the editorial board. On a personal level, fulfilling this leadership role taught me so many skills. First and foremost, communication is key. A team is able to work well together only through good communication. Also, whether you are leading a sports team or a group project, you should always ask for feedback and encourage others to do the same.

While you and everyone around you are trying their best, things still can go wrong. Try to make the best of it and do not put too much focus on the negatives. Something else I learnt is, in the end, it will all somehow work out. Do not stress too much, a little bit is more than enough!

To mark this occasion, we hope you will enjoy this special edition on mental health. The Zebra of Medicine will compare heart attacks with panic attacks. Those are two different diseases; however, they have similar symptoms. How do you recognise the difference? Furthermore, we will discuss the effect of early life stress on amygdala and prefrontal cortex connectivity. Lastly, have you always wanted to know how many hours of sleep are really necessary? Wondering why you are always waking up tired even though you think you got enough sleep? Keep on reading!

We could not let you go without mentioning the disease that had Europe and the whole world halt everyday life as we knew it. Yes, I mean COVID-19. Exams were cancelled, schools closed and borders shut down. The lockdown that lasted several months changed everyone's perspective on life completely. So do not be too harsh on yourself if your internship got cancelled, your exchange plans have been postponed or your graduation ceremony has been delayed. You just survived a global pandemic.

Yours faithfully,

Mariam Baghdady
Chair Editorial Board

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EARLY LIFE STRESS LEADING TO OPPOSITIONAL BEHAVIOUR VIA THE AMYGDALA-PREFRONTAL CIRCUIT

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Insights

There is no standard and correct way to raise a child. Even when you try your best to give them all the care they need, there are many uncontrollable aspects that could affect a child's upbringing, ultimately affecting adulthood. These aspects range from their genetic background to environmental challenges, such as a traumatising event. Researchers have found that children who are exposed to these high stressors are more likely to become aggressive. Interestingly, this is not just due to the emotional effect of the event. It has been described in literature that a structural change in the brain due to exposure to stress could also lead to oppositional behaviour. This article will dive more into detail on what is known about the effect of exposure to high stressors in childhood on the brain, resulting in different types of aggressive behaviour.

Introduction

Early life stress (ELS) can be identified as child maltreatment or chronic poverty with behavioural problems [1]. Exposure to ELS could lead to long-lasting emotional difficulties and aggressive behaviour in adulthood [2]. Besides, it has become evident that ELS is associated with a higher incidence of mental health problems across the lifespan [2]. This oppositional behaviour is caused by compromised brain development due to ELS [3]. It is therefore crucial to investigate the possible neurobiological mechanisms that are involved in this increased risk for psychopathology. Important regions involved in emotion regulation, threat-reactivity and aggression are the prefrontal cortex (PFC), hippocampus and amygdala [1]. While the amygdala and hippocampus are directly associated with this regulation of emotions, the PFC is thought to regulate the activity of the amygdala creating an amygdala-PFC circuitry [4]. Studies suggest that a change in this amygdala-PFC circuitry could affect oppositional behaviour [2]. Therefore, in this paper the effect of ELS on the amygdala-PFC circuitry resulting in different types of aggression will be discussed. Besides focussing on the environmental aspect, we will also elucidate the genetic contribution to this phenomenon.

Amygdala and the PFC in ELS and aggression

Before studying the connectivity between brain regions, it is essential to understand the involvement of the separate brain structures in ELS and aggression. The amygdala is crucial for the modulation of emotion-related behaviour. Therefore, to understand the effect of ELS on the onset of behavioural problems, it is important to first understand more about this small region in the temporal lobe [5].

Considering that the amygdala plays a key role in processing emotions, it was suggested to be an area that causes aggression. Interestingly, a change in amygdala activity can result in two different types of aggressive behaviour, of which one is associated with increased amygdala activity, and the other one with decreased activity [6]. When an individual has increased responsiveness of the basic threat circuit, they will respond to a threat in a more reactive manner, which includes unplanned, enraged attacks on the source of threat or frustration (reactive aggression) [7]. On the other hand, decreased amygdala responsiveness is associated with psychopathic traits, such as deficits in emotional empathy and a reduction in the processing of distressing factors [8]. Such an individual is more likely to harm others in order to achieve their goals (proactive aggression). Therefore, when talking about the effect of the amygdala on aggression, a distinction must be made between these two different types.

Multiple retrospective studies found that people exposed to ELS have a heightened amygdala reactivity to emotional cues, suggesting that the amygdala reactivity increases with stress-related signals [9-13]. Moreover, a number of different types of ELS, such as sexual, physical and domestic violence, were linked to a volume expansion of both left and right amygdala alongside increased glucocorticoid levels [14, 15]. Ultimately, this increased amygdala reactivity was also associated with more reactive aggressive behaviour [16].

Besides the amygdala, the PFC also plays a crucial role in the modulation of aggression. A meta-analysis revealed that prefrontal and structural impairments significantly resulted in antisocial behaviour [17]. Furthermore, people subjected to ELS had an accelerated amygdala-PFC connectivity development, resulting in a significantly early shift to the mature amygdala-PFC connectivity [18]. This could lead to more oppositional behaviour, since the PFC has less control over the amygdala responsiveness, due to the loss of connectivity (Figure 1).

Since there is a conspicuous link between both structures that is affected by impairment, studying the effect of different aspects on this circuitry will contribute to our understanding of ELS and aggression. While ELS is an important risk factor for the development of behavioural problems, this does not mean that it invariably leads to this dysfunction [19]. The different outcomes can be explained partially by the interactions of genetic and environmental factors: a person's mental state is usually healthy when exposed to low environmental stressors. However, it will become impaired when the person has to deal with high stressors. While environmental stress by itself could decrease the normal functioning, the genetic background can make a person more resilient or vulnerable to these environmental stressors [19].

Environmental factors in ELS

In humans, the amygdala-PFC circuitry undergoes age-related changes across childhood, adolescence and young adulthood. Evidence from multiple animal species showed that the amygdala-PFC circuitry is highly sensitive to environmental inputs, especially during the early life of an organism [18]. Examples of environmental inputs, besides age, that could affect the outcome are sex and the type of event.

When one compares the connectivity of previously institutionalised children to typically raised children, apparent differences are found.

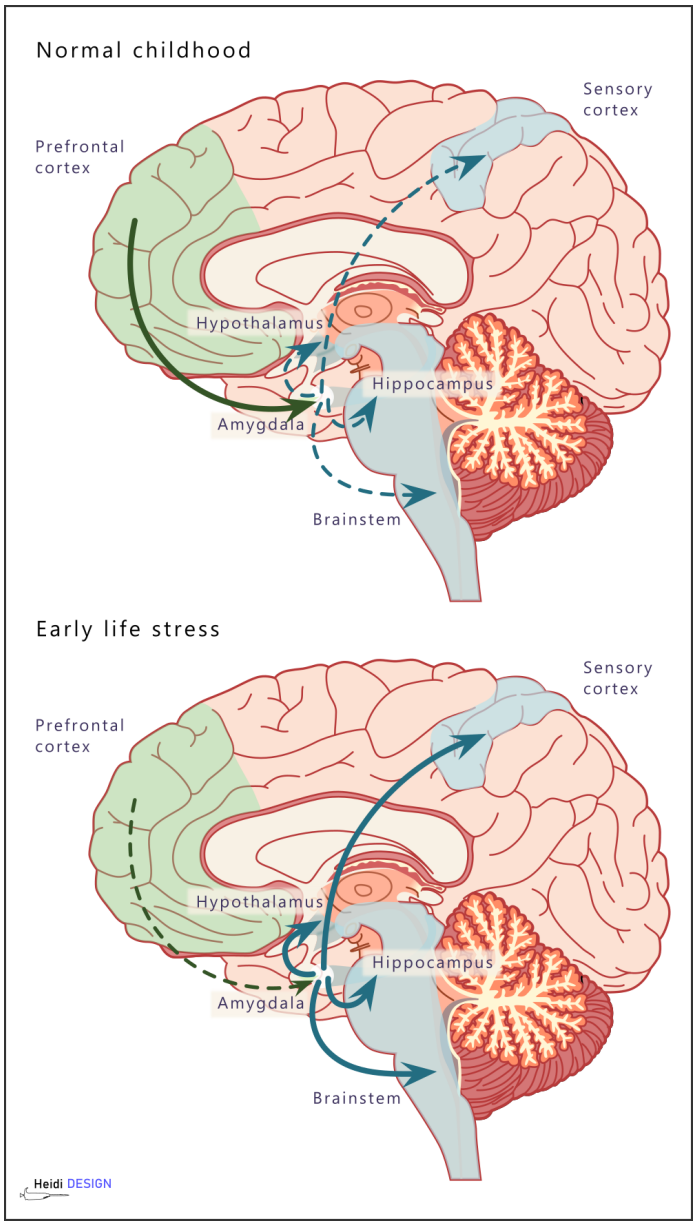

Figure 1: Reduced top-down regulation of amygdala as a result of decreased PFC-amygdala connectivity

Early life stress can decrease the connectivity between the PFC and amygdala. This affects the emotional circuitry, since an important role of the amygdala is to communicate with the hypothalamus, the sensory cortex, the brain stem and the hippocampus. When top-down regulation of the amygdala is reduced, this will ultimately affect the beforementioned structures. This is associated with an increase in oppositional behaviour.

Usually, untraumatised children show a positive connectivity between the amygdala and PFC, which switches to a more adult-like phenotype around ten years of age. This results in a negative connectivity in adolescence. Interestingly, the previously institutionalised children already showed this negative connectivity in their early life. This early shift results in a change of the amygdala and PFC structure compared to typical children [20].

Another study observed that the age of the child and the type of abuse is important for the amygdala sensitivity later in life and the functional connectivity with the PFC [21]. Peer emotional abuse of 15-year-olds is associated with a reduced amygdala volume and increased activation, resulting in reactive aggression. In contrast, parental physical abuse is a primary risk factor around the age of four, resulting in enhanced amygdala volume (proactive aggression) [21]. This suggests that there are developmental differences after maltreatment concerning the amygdala, the PFC connectivity and the type of aggression when looking at age and the type of abuse.

Besides age, the activation of the PFC after ELS is also moderated by sex in early adolescence [19]. Colich *et al.* showed that compared to males, females had an increased association between ELS and PFC activity. However, when studying the PFC-amygdala connectivity, no significant difference was found between sexes, as they both showed a negative correlation between connectivity and ELS severity (more ELS results in less connectivity) [22]. Another study showed that females in their childhood have higher cortisol levels, which will lead to more negative connectivity compared to males. However, the causal relationship between these factors remains unknown [23].

Genetic factors in amygdala-PFC connectivity

Genetic factors also have an important effect on our behaviour. Extensive research found that genetic variations in the serotonin transporter (*5-HTTLPR* polymorphism) and monoamine oxidase A (*MAOA*) are able to modulate amygdala functioning and its connectivity with the PFC. These variants were found to predispose the increased aggression [24]. In rhesus monkeys, the common polymorphism of *5-HTTLPR* is associated with an increase of amygdala activation and an increase in aggressive behaviour [25].

A common polymorphism in the *MAOA* gene that is also associated with aggression is the *MAOA-L* variant, the variable-number tandem repeat in the upstream region of the gene. The low expression variant of *MAOA* predicted limbic volume reductions and a hyperresponsive amygdala compared to the high expression allele [26]. A study by Buckholtz *et al.* suggests that there is a strong influence of sex on these genetic effects, showing a neurobiological susceptibility of the effect of the low expression variant in men [27].

Discussion

From this overview can be concluded that there is a neurodevelopmental mechanism by which ELS in childhood can affect the amygdala-PFC connectivity resulting in different behavioural problems. A decreased connectivity results in a reduced top-down regulation of the PFC on the amygdala, resulting in more aggressive behaviour. As discussed, age, sex, the type of abuse and common polymorphisms in itself are important modulators for the connectivity and ultimately the type of aggression. Interestingly, the combination of the aforementioned factors also has a strong influence on the susceptibility. Therefore, we can conclude that the risk of onset of aggression after exposure to ELS is affected by a strong interaction of both environmental and genetic factors.

However, a lot still remains unknown about the exact influence of these interactions on the connectivity between the amygdala and the PFC. These knowledge gaps leave room for interesting studies that could still be conducted. First, it would be of interest to study whether the amygdala-PFC connectivity could be used as a possible biomarker to treat people with oppositional behaviour in an early stage. Furthermore, since it was found that age, sex and the type of abuse are important modulators, studying whether adjustment of treatment schemes would be beneficial to fit the sensitive periods for males and females at certain types of abuse at certain ages is a promising step forward.

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MYTH OR SCIENCE?
THE IMPORTANCE OF SLEEP QUALITY:
AN INSIGHT INTO THE RELATIONSHIP BETWEEN SLEEP DURATION AND SLEEP QUALITY

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Critical Appraisal

It is four o'clock in the morning and you are still partying with your friends. Suddenly, you realise that it would be wise to go home and get some sleep. After all, you have an important class tomorrow. Three hours later, your alarm clock goes off, you wake up and you miraculously feel fit. Most students are familiar with such a situation. Students tend to love partying through the night, ultimately skipping many hours of sleep. Despite the short night, some of them manage to feel fit after having been deprived of sleep. An incredible feat as one should sleep between 7 and 9 hours every night, according to the American Academy of Sleep Medicine [1]. This discrepancy questions the relationship between sleep duration and sleep quality, which will be explored in this article.

Introduction

According to the American Academy of Sleep Medicine, the recommended sleep duration to achieve optimal health for adults is between 7 and 9 hours [1]. Adolescents should sleep longer, ideally between 8 and 10 hours [1]. The important role of good sleep in optimal health and well-being has been increasingly recognised [2]. However, many people do not get the sleep they need and are thus likely to suffer from suboptimal health. Interestingly, a lot of people still feel tired despite sleeping a sufficient amount of hours. This phenomenon raises the question of how much total sleep time (TST) contributes to the degree of wakefulness after sleep. In this article, we aim to give perspectives on the role of TST in the wakefulness after sleep. To answer this question, we will first explore the concept of sleep quality by analysing the contributing factors. The article will then discuss ways to measure sleep quality and the influence of circadian rhythms. Finally, possible manners of optimising one's sleep will be considered.

Sleep quality

Sleep quality is a widely used concept in both the clinical and research context. Nonetheless, a clear definition is absent [3]. An approach to defining this concept is to self-rate the quality of sleep [3]. However, people are unable to observe their own sleep, as they lose their consciousness during the process. Another approach is to divide sleep quality into objective, measurable components. In 2017, the National Sleep Foundation (NSF) tried this approach and came up with guidelines for sleep quality [3]. The components they found can be divided into three categories: sleep continuity, sleep architecture and naps.

Sleep continuity is comprised of sleep latency, awakenings of more than 5 minutes, wake after sleep onset (WASO) and sleep efficiency. Sleep latency is the time from trying to sleep until sleep onset, with a latency shorter than 15 minutes indicating good sleep [3, 4]. Fewer than two awakenings longer than 5 minutes is considered good sleep [3]. For adults older than 65 years, two awakenings were also deemed acceptable [3]. WASO is the wake time between sleep onset and final awakening, which should be shorter than 20 minutes in order to be considered good sleep [3, 5]. Lastly, sleep efficiency is commonly defined as either the ratio between TST and time in bed or the ratio between TST and time trying to sleep, the latter generally giving a higher ratio [5]. An efficiency above 85 percent was found as an indicator of good sleep quality [3].

The sleep architecture measurements include the time of the TST a person spends in each of the different stages of sleep: rapid eye movement (REM) and three stages of non-rapid eye movement (N1-3) sleep. For adults, good sleep should be comprised of 21 to 30 percent REM sleep [3]. N1 sleep should be less than 5 percent of TST and N3 sleep should be 16 to 20 percent of TST [3]. N2 sleep is not an indicator of good sleep, but more than 81 percent of N2 sleep indicates bad sleep quality [3]. The percentages differ per age group.

In the third category the naps per 24 hours, nap duration and nap frequency are investigated. Naps are episodes of sleep outside the principal sleep period. For school-children and young adults, no naps indicate good sleep quality but for teens one nap does [3]. For all age groups taking more than four naps a day is not considered good sleep quality [3]. A nap duration shorter than 20 minutes indicates good sleep quality but a duration longer than 100 minutes does not [3]. Naps can be an indicator of bad sleep, but can be present in people with good sleep quality.

Although not mentioned in the NSF recommendations, TST is also often considered as a part of the objective components of sleep quality. Hirshkowitz *et al.* acknowledged the importance of sufficient sleep duration, stating that an adult needs 7-9 hours per night, decreasing with age [6]. The before mentioned recommendation from the American Academy of Sleep Education mentions the same numbers [1]. Importantly, the necessary duration of sleep varies per individual [6]. Alertness during the day indicates sufficient sleep duration [6]. In certain individuals, 6 hours can be enough sleep [6].

Measuring sleep quality

The use of polysomnography (PSG) dates as far back as 1937 when the first sleep recording, using an electroencephalogram (EEG), was published [7]. PSG measures neurophysiologic, cardiopulmonary and other physiologic parameters during sleep. A standard PSG includes EEG, electrooculography, electrocardiography, and electromyography of the chin [7]. In certain diseases such as obstructive sleep apnea, central sleep apnea and periodic limb movement, clinical applications including recordings of airflow, respiratory effort, limb electromyography and oxygen saturation can be measured as well [7]. PSGs are mainly used to diagnose sleep-related breathing disorders, such as obstructive sleep apnea and central sleep apnea [8]. It can also be

used to diagnose sleep-related seizures, periodic limb movement disorder and parasomnias.

The main downside to PSG is its limited use outside of the laboratory, as a sleep technologist is required to set up equipment and apply electrodes to the patient [9]. This limitation led to the development of alternatives. Wrist actigraphy is the most frequently employed alternative for PSG. However, there are also several wearable EEG systems [9]. Actigraphy uses activity trackers containing accelerometers that record movement of the wrist at regular intervals. Using this data, sleep/wake status can be estimated. Kosmadopoulos *et al.* showed that, compared to PSG, wrist actigraphy is more suitable for predicting sleep but not wake [10]. The EEG systems could in theory be more accurate than actigraphy as they can also measure biosignals like heart rate and temperature, along with activity [11]. However, more research is needed to fully adopt these devices [11].

In 1989, Buysse *et al.* developed the Pittsburgh sleep quality index (PSQI) [12]. This self-rated questionnaire, used to assess sleep quality, is comprised of 19 questions for the patient and five questions for the roommate or bed partner. These 19 questions assess a wide variety of sleep quality related factors, including estimates of sleep duration and latency, and the frequency and severity of sleep-related problems [12]. The score of the PSQI ranges from 0 to 21, retrieved by grouping the 19 items into seven component scores, each getting a score from 0 to 3. The lower the score, the better the sleep quality. In their research, Buysse *et al.* showed that the PSQI was easy to use, stable over time and can discriminate patients from controls [12]. A meta-analysis from 2016 acknowledged the PSQI as the only standardised clinical instrument to assess a wide range of factors relevant to sleep quality [13].

Lastly, smartphone applications are increasingly used across the world. In 2014, Sleep Tracker and Alarm Clock were the most downloaded applications on iPhones, with over 500 applications available in the app store [14, 15]. Bhat *et al.* found that these applications are as good as PSG in the detection of sleep time, but are less precise in distinguishing the different stages of sleep [16]. Furthermore, compared to actigraphy, the applications are more sensitive to changes in the environment, such as the presence of a partner or the place of the smartphone on the mattress [15].

Influence of the timing of waking up

The circadian clock plays a crucial role in several processes in the body to ensure appropriate body function during the different hours of the day [17]. The circadian rhythm is regulated by a brain region called the suprachiasmatic nuclei [18]. Sleep is one of the components regulated by this internal clock. Light is the best known external regulator of the rhythm [19]. There is a spectrum of different chronotypes, ranging from early types on the one end to late types on the other end, which varies among individuals [17]. These chronotypes influence our body's ideal bed and wake times and are determined genetically [20]. This can lead to several problems in our 'nine to five society' as the chronotype of the individual might not align with the demands of society. It is possible to shift the circadian rhythm by regulating one's exposure to light and can be severely disrupted by changes in light exposure [17]. Low light levels in nursing homes, severe eye damage such as blindness and working night shifts are a few examples [21-23].

Creating conditions for optimal sleep

The recent guidelines from the NSF suggest that sleep quality can be improved at all ages by improving sleep continuity (decreasing sleep latency, nighttime awakenings and WASO) and sleep efficiency [3]. In contrast, the influence of sleep architecture and naps on sleep quality is less clear [3]. Healthy sleep habits (Figure 1) are of value in optimising good sleep quality [24]. The sleep environment should be cool, dark and comfortable [25, 26]. A regular sleep/wake schedule, in which consistent

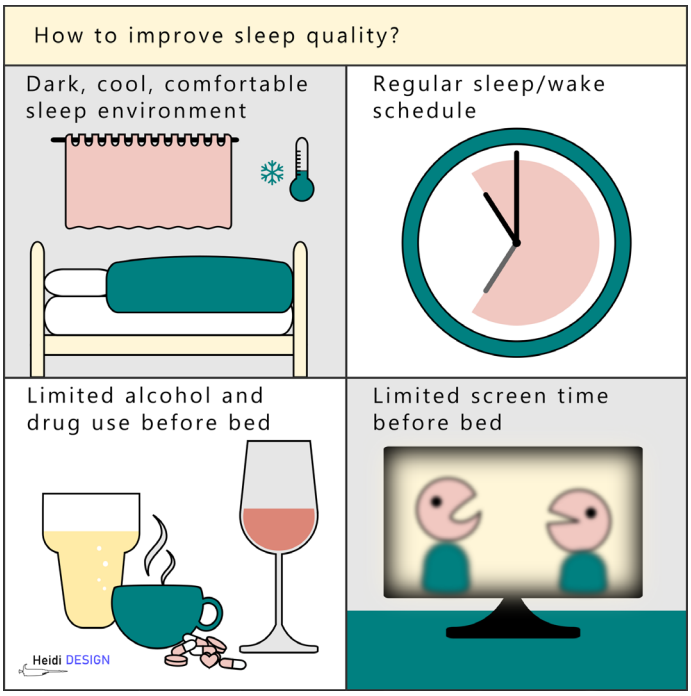

Figure 1: Factors that improve sleep quality
Sleep quality can be improved by changing one's sleep habits. The conditions for healthy sleep include: a dark, cool and comfortable sleep environment; a regular sleep/wake schedule; limited use of alcohol and drugs before bed; and limited screen time before bed.

wake times is the most important, aids to good sleep quality [24, 27]. Substance use, such as caffeine and alcohol, should be limited some hours before bed (3-7 hours for caffeine and 3-4 hours for alcohol), as they can interfere with sleep [28, 29]. Screen use 1-2 hours before bed can influence melatonin release and should thus be avoided [30]. Improvements in sleep duration and quality appear to improve reaction time, accuracy, and endurance performance [31]. In contrast, poor sleep may increase the risk of injury and illness, and may undermine overall health [31].

Conclusion

To conclude, sleep duration is an important part of good sleep and one should aim for around 7 to 9 hours per night. However, sleep quality is more than that. Sleep continuity, sleep architecture and the number of naps are important indicators as well. Sleep can be measured objectively via PSG and actigraphy and subjectively via the PSQI. Smartphone applications are very popular for measuring sleep, but are not yet as accurate as the other methods. Wakefulness can also be influenced by disruptions in the circadian rhythm, which is the internal clock of the body. Sleep quality can be increased by improving sleep continuity and efficiency as well as by adopting healthy sleep habits. Thus, to feel awake in the morning, one should take into account more than just sleeping for 8 hours each night.

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THE GOOD MICROBES: IMPROVING MENTAL HEALTH THROUGH THE MICROBIOME?

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Critical Appraisal

Already in 1910, George Porter Phillips, physician at London's Bethlem Royal Hospital, stated that: "ranging from a mild attack of depression to a severe case of melancholia, one finds the hub of the disturbance centring itself in the alimentary canal" [1]. He was not alone in this view, as at the beginning of the 20th century, physicians and researchers started to see connections between gastrointestinal and psychological disturbances. Among them was Nobel prize winner Metchnikoff, who recommended to treat such disturbances by taking large quantities of certain microbes, for example, by drinking sour milk [2]. This was in line with his famous belief that we could "modify the flora in our bodies and replace the harmful microbes by useful microbes" [2]. However, their research was mainly hypothetical and small-scale. Not enough scientific support was reached and the idea of microbes influencing our mental health became a taboo until the end of the century [3]. It would take technological developments, such as metagenome sequencing of microbes, and controlled clinical trials, to start up building the scientific capacity and support to bring the fields of microbiology and psychiatry back together. These days, physicians find themselves asking once again: could certain microbes help in treating a patient's depression [4]?

Introduction

Worldwide, mental disorders have a significant consequence on health. According to the World Health Organization, the single largest contributor to global disability is depression [5]. Estimates of the number of people with depression exceed 300 million, with major depressive disorder (MDD) affecting one in five people at some point during their lifetime [5-7]. The MDD symptoms and their severity vary, but often involve decreased energy, low mood, loss of interest and enjoyment, thereby impairing daily functioning and quality of life [5, 8]. Although various pharmacological treatments for MDD are at hand, they can have serious side effects and only 60-70% of patients respond, in various degrees [9]. Therefore, further insight into the complex pathophysiology of MDD is needed to open up the way for new leads of therapy. One of the promising areas of research is the gut microbiome, where the first clinical trials modulating this microbiome have started to show the improvement of depressive symptoms.

The microbiome-gut-brain axis

We have a long and complex history with the microbes living within and on us. According to current estimates, we contain at least as much microbial as human cells [10]. Although these microbial inhabitants have not always been appreciated, we now start to realise more and more how crucial they are to our health and well-being. Our gut microbes perform various physiological roles. Among the first to be elucidated were their abilities to break down indigestible food and to protect against (opportunistic) pathogenic microbes [11]. Even more complex roles were described over the last few decades. As it turns out, our gut microbes can also interact with our central nervous system (CNS). This bidirectional microbiome-gut-brain axis consists of various neural, endocrine, metabolic and immune signalling pathways (Figure 1) [12]. Although the underlying mechanisms are not fully elucidated yet, some interesting examples can already be given. One example is the direct influence of gut microbes on the signalling in the enteric nervous system, that is connected to the CNS through the vagus nerve [13]. Other gut microbes influence the endocrine hypothalamic-pituitary axis involved in cortisol production, thereby altering the stress-response [14, 15]. Regarding metabolic pathways, gut microbes are involved in the production and degradation of neuroactive compounds and their precursors, such as tryptophan, the building block for serotonin [16]. A new mechanism recently proposed involves short-chain fatty acid (SCFA) production by the gut microbes, that can act as epigenetic modulators. When these SCFAs reach the brain, they could alter the gene expression of brain cells, potentially influencing a multitude of processes [17]. The microbiome also affects the production of cytokines, which can induce inflammation in the brain when acting on microglia [18, 19]. Moreover, there is communication from the central nervous system back to the gut as well [20]. Through the release of neurotransmitters and hormones, the gut habitat and physiology can be changed, affecting the microbiome composition.

The 'depressed microbiome'

As gastrointestinal and mental health problems often coincide, extensive research has been performed on this connection. With the developments of DNA sequencing techniques, we are now able to identify and characterise the gut microbes and many correlation studies are performed to see whether specific microbes can be associated with specific (medical) conditions. However, research on the directionality of this relation has been limited mainly to animal models, which cannot be translated directly to human health. A remarkable example is given by faecal microbiota transplantation (FMT) studies in mice and rats, where FMT from MDD patients induced dysregulated microbiota in the animals. The developed inflammation and anxiety-like behaviour points towards a causal connection [21, 22]. In humans, studies on the connection between the gut microbiome and mental health have been mainly associative of nature. Although many have focused on depression, a recent meta-analysis showed that based on taxonomy, no consensus can be reached yet on what makes the 'depressed microbiome' [23]. In the taxonomy studies, only one gene is used to identify the bacteria. This strictly prokaryotic gene encodes for the 16S ribosomal RNA (16S rRNA), which is highly conserved in function. Therefore, small differences in the 16S rRNA sequence can be used to identify the different bacterial

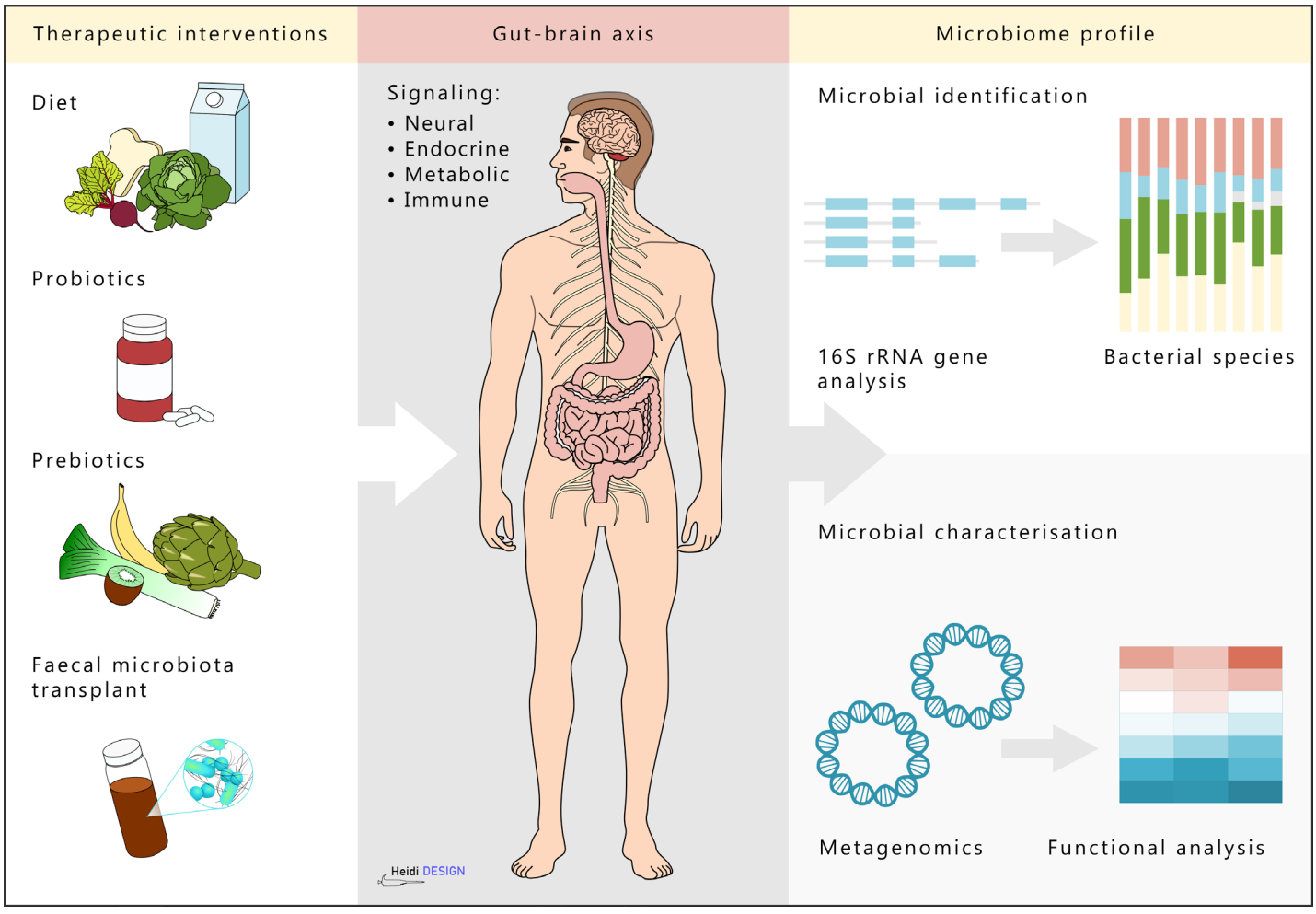

Figure 1: Overview of signalling along the gut-brain axis together with the therapeutic interventions to alter and the methods to profile the gut microbiome
The gut microbiome composition plays a significant role in gut-brain signalling and can be altered through various interventions. These include specific diets, the direct intake of certain microbes (probiotics) or their nutrients (prebiotics) and faecal microbiota transplants. Signalling along the gut-brain axis involves various nerves, hormones, neurotransmitters and cytokines that all contribute to the versatile and extensive communication between the gut microbiome and the central nervous system. The gut microbiome can be profiled through sequencing of only the 16S ribosomal RNA, allowing for taxonomic analysis, or through the total of bacterial genes (metagenomics), allowing for functional analysis.

taxa. As no specific bacterial taxa can yet be pointed out to be the most relevant to depression, it has been suggested that studies of microbial functioning could complement in understanding the gut microbiome in depression [23]. While taxonomic analyses rely on the identification of solely the 16S rRNA genes to identify which bacteria are present, functional metagenomics takes the entire genome of bacteria into account (Figure 1). In this way, the functional potential of the bacteria, including neural, endocrine, metabolic and immune signalling, can be predicted [23-25].

One of the first studies to look at this functional potential as well is the impressive Flemish Gut Project, with over a thousand of our Belgian neighbours participating [24]. Within this cohort, Belgian and Dutch researchers looked at the associations between gut bacteria, their metabolic potential and the quality of life (QoL). The QoL was assessed with an extensive survey, covering both mental health concepts, such as emotional well-being, and physical health concepts, such as vitality. When first taking a taxonomic approach, they found that certain bacteria, such as *Faecalibacterium* and *Coprococcus*, known for involvement in intestinal barrier function and inflammation, were associated with a higher QoL, while *Dialister* and *Coprococcus* were decreased in participants with depression. Moreover, the researchers looked at the functional potential, by associating the QoL with defined 'gut-brain modules', which are based on microbial pathways of neuroactive potential. With this approach, they found a connection between QoL and the dopamine metabolism of a gut microbiome, more specifically its metabolite 3,4-dihydroxyphenylacetic acid, also known as DOPAC, pointing towards a new target for treatment.

Treating the microbiome

Ever since the first indications of the gut microbiome influencing mental health, people have been trying to mitigate mental health disturbances through alterations of the microbiome [3]. Although no consensus has been reached on the bacterial taxa most relevant to depression, many treatments to improve depressive symptoms through the microbiome have been suggested. Such treatments include certain diets, probiotics, prebiotics and even FMT (Figure 1) [4].

As diet seems to be the major determinant of gut microbiome composition in adults, restriction to a certain diet may change the

microbiome in a beneficial way in terms of gut-brain communication [26]. Although the potential of such nutritional interventions is still under debate, several attempts to show its potential have been made with large trials. An example is the "Supporting the Modification of lifestyle In Lowered Emotional States" trial, also known as SMILES, where adults with MDD switched to a Mediterranean diet for 12 weeks [27]. The Mediterranean diet, with abundant fruits, vegetables and grains, is believed to be a healthy, anti-inflammatory diet and is associated with a lower risk of depression. The 12-week intervention was indeed reported to alleviate MDD symptoms, but other researchers say that the large effect sizes are in part attributable to the study design and therefore, should be critically reviewed [28].

Besides changing the overall diet to alter the gut microbiome, one could also directly take the microbes that confer a health benefit or take certain nutrients, such as fibres, that specifically enhance their growth. These are, respectively, termed probiotics and prebiotics. Many studies on their use in mental health have been performed, but differ in study design, including the type, dose and duration of pre-or probiotic treatment, the cohort, the read-out of depressive symptoms and many more. Meta-analyses of these controlled trials report that, although prebiotics do not significantly mitigate depression, probiotics can positively affect depressive symptoms [29, 30]. Over the last years, it has, therefore, become widely accepted that at least some probiotic treatments can help in reducing the depression burden [29-32]. To help clinicians and patients in their search for these scientifically proven treatments, the International Scientific Association for Probiotics and Prebiotics offers a clinical guide [33].

Another suggested treatment is the FMT, where the faecal microbiota from a healthy donor would be given to an MDD patient. The FMT was first reported in medical literature in 1958 and is best known for its treatment of *Clostridium difficile* enterocolitis [34, 35]. Currently ongoing clinical studies on FMT in MDD have yet to be completed before data on its effectiveness can be analysed. However, similar studies in inflammatory bowel syndrome patients seem promising. Patients with this syndrome that received a healthy donor FMT showed improvement in terms of depression and anxiety [36]. Yet, it should be noted that it is currently not clear whether it is mainly the microbes themselves, certain bacterial products or even bacteriophages, mediating these effects [37].

Limitations

Although research in animal models and the first human studies may look very promising, caution is warranted as well. Critical evaluation of study design is required to assess the value of given results and their translation to specific patient groups. For example, the famous Yakult bacterium *Lactobacillus casei Shirota* as probiotic intervention only showed mood improvements for those people at the lowest end of the mood scale [38]. Therefore, researchers in the field emphasise that it is of great importance to be aware of the selected participants of each study [29]. The inclusion of healthy participants that have little room for improvement in terms of depressive symptoms may limit evidence for a real antidepressant potential in patients or sub-clinical populations. The performed human trials also vary in the exact treatment type, for example the (combinations of) bacteria strains in probiotic studies, the dosage and duration and the way in which depression severity is assessed. Moreover, many studies are too small in size or do not account for confounding factors such as diet, medical comorbidities and medication impacting the gut microbiome, including antibiotics [23, 24, 32]. Only when cohorts are large enough to control for confounding factors and the above-mentioned parameters of study design become more standardised, will clinical trials be able to give conclusive results.

Conclusion

More than a century after the ideas of Porter and Metchnikoff a crucial role for the gut microbiome in our mental health can no longer be denied. These microbes influence our central nervous system through various neural, endocrine, metabolic and immune signalling pathways. Specific microbiome features have been linked to depression and gave way to new targets for treatment such as probiotics. Although animal studies look very promising in terms of causality and treatment successes, human studies are lagging behind. Only with standardised large clinical trials can the role of the microbiome and the effectiveness of microbiome-targeting treatments in human mental health be fully elucidated.

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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

The cerebral lobes cannot only be distinguished by anatomical location, but also according to their function. In which lobe can the primary motor cortex be found?

A. Frontal lobe
B. Parietal lobe
C. Temporal lobe

(Topic from Q6-1 MGZ Nervous System, 2018)

Question 2

After a stroke, a patient suffers from paralysis of their right hand. The mobility of the hand is controlled by a nerve tract emerging from the contralateral motor cortex of the brain. In what structure of the central nervous system does this nerve tract cross to the contralateral side of the nervous system?

A. Capsula interna
B. Medulla oblongata
C. Spinal cord
D. Thalamus

(Topic from Q6-2 MGZ Nervous System, 2019)

The answers to these questions can be found on page 17 in this journal.

ZEBRAS OF MEDICINE
HEART ATTACK VS. PANIC ATTACK: TO PANIC OR NOT TO PANIC?

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Abstract

Background: Acute myocardial infarction (MI) is a life-threatening event defined as myocardial necrosis due to ischaemia. A panic attack is a sudden episode of fear that may include physical symptoms. Symptoms associated with acute MI show a substantial overlap and similarity with symptoms presented in a panic attack. This makes it difficult for patients and doctors to distinguish one from the other, especially since symptoms vary between individuals for both MI and panic attacks.

Objective: The aim of this review is to delineate the characteristic properties that could enhance differentiation between the symptoms of MI and panic attacks.

Discussion: Chest pain or chest discomfort is a core symptom of MI, but is also featured in 70% of panic attacks. Other shared symptoms are dyspnoea, nausea, diaphoresis (sweating), palpitations, feeling light-headed, and paraesthesia. Symptoms that are associated with panic attacks, but are not characteristic for MI, include chills or heat sensations and trembling, as well as derealisation and depersonalisation. Back pain, which is frequently found in MI patients as part of chest pain radiation, is not related to panic attacks. Fatigue is distinctive for MI and is not associated with panic attacks. A panic attack typically peaks within a short period (<10 minutes), whereas symptoms accompanying MI are generally more persistent (>20 minutes). Non-anginal chest pain is more associated with panic attacks, whereas anginal chest pain is more suggestive of MI. Typical angina can also occur in patients with panic disorder (PD), and patients with acute coronary syndrome (ACS) can have atypical presentations of MI.

Conclusion: The diagnostic performance of chest pain characteristics is limited, but several discriminative differences between acute MI and panic attacks exist. Further diagnostic testing is mandatory for every patient with acute prolonged chest pain. Since PD and ACS can co-occur, and symptoms of both MI and PD have an interindividual presentation, acute causes of chest pain should not be excluded in the evaluation of psychiatric disorders for patients presenting with chest pain.

KEYWORDS: myocardial infarction, acute coronary syndrome, panic disorder, chest pain, clinical presentation

Introduction

Acute myocardial infarction (MI), also known as a heart attack, is defined as myocardial cell death due to ischaemia (inadequate oxygen supply) [1]. MI is classified under the term acute coronary syndrome (ACS) [4]. ACS refers to a number of conditions associated with abruptly reduced blood flow to the heart, ranging from unstable angina pectoris (UAP) to acute MI (Figure 1) [1]. Based on ECG characteristics, acute MI can be designated as either ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (non-STEMI) [1]. STEMI is the result of complete coronary artery occlusion, whereas non-STEMI is usually caused by partial occlusion of the artery [1]. Thus, ACS includes the following three clinical manifestations: STEMI, non-STEMI, and UAP [1].

In addition to these categories, MI (STEMI/non-STEMI) can be further classified into five different subtypes, of which type 1 and 2 are the most important [1]. A type 1 MI is caused by athero-thrombotic artery disease and is typically precipitated by atherosclerotic plaque disruption [1]. In type 2 MI, an acute stressor may lead to myocardial injury resulting from an imbalance between oxygen supply and demand [1].

The most prominent symptom featured in MI is chest pain or chest discomfort. Another phenomenon in which chest pain or discomfort can occur is a panic attack, which is experienced by at least 10% of the general population once in their lifetime [2]. A panic attack can be described as a sudden episode of intense fear or discomfort, often reaching a peak within 10 minutes [2]. Besides psychiatric symptoms as derealisation, fear of losing control, and fear of dying, panic attacks are also associated with several cardiopulmonary, autonomic, neurologic, and gastrointestinal symptoms, including chest pain or chest discomfort [3]. The traditional clinical classification of chest pain describes three types: typical angina, atypical angina, and non-anginal chest pain [4]. Typical angina is characterised by substernal chest discomfort, precipitated by exertion or emotional stress and relieved by rest or nitroglycerine within minutes, whereas atypical angina meets two out of these three criteria [4]. Chest pain is considered non-anginal when it meets one or none of the characteristics [4].

Even though MI can be lethal and a panic attack is not life-threatening, both entities have a substantial overlap in symptoms. Therefore, it can be challenging for patients and doctors to distinguish one from the other, especially since symptoms differ between individuals for both MI and panic attacks. This review aims to delineate the characteristic properties of MI and panic disorder (PD) that could enhance differentiation between the two fundamentally different diagnoses.

Table 1: Similarities and differences in symptoms of myocardial infarctions and panic attacks

Myocardial infarction	Panic attack
Chest pain or discomfort	Chest discomfort
Nausea or vomiting	Nausea or abdominal stress
Light-headedness or syncope	Feeling dizzy, unsteady, light-headedness or syncope
Diaphoresis (sweating)	Diaphoresis (sweating)
Paraesthesia (numbness or tingling sensations)	Paraesthesia (numbness or tingling sensations)
Dyspnoea	Sensations of shortness of breath or smothering Feelings of choking
Palpitations	Palpitations, pounding heart or tachycardia
Sense of doom	Fear of dying Fear of losing control or going crazy
Fatigue	*Derealisation (feelings of unreality) or depersonalisation (being detached from oneself)*
Discomfort or pain in arms, shoulder, neck, back or jaw	*Trembling or shaking*
	Chills or heat sensations

Clinical presentation

In patients suffering from MI, chest pain is often similar to anginal pain, but there are some differences. These patients may experience more severe, longer-lasting (for over 20 minutes) chest pain which is not relieved by rest or nitroglycerine within minutes. It is often described as a dull pressure sensation that may also be perceived as squeezing and may radiate up to the neck, left arm (less frequently to both arms or to the right arm), shoulder, neck, jaw, and back [4]. Pain in the upper back, arm, neck, and jaw are more often reported by women when compared with men [4, 5]. Chest discomfort might present itself in combination with diaphoresis (sweating), nausea, dyspnoea, or abdominal pain [6]. Atypical presentations such as indigestion-like symptoms, epigastric pain, dyspnoea, fatigue, palpitations, and light-headedness (with or without syncope) are more frequently reported by women, diabetics and elderly [5].

Research found that up to 70% of panic attacks feature chest pain as a symptom as well [7]. In general, panic attacks are associated with non-anginal chest pain, often described as aching or stabbing in character. In one study, 91% of individuals diagnosed with an anxiety disorder reported atypical chest pain [8]. Among these patients, palpitations were the most frequently associated symptom, followed by dyspnoea, fear of dying, dizziness, and chills or heat sensations [8]. However, it is essential to note that panic attacks can occur with typical angina as well [5].

Symptoms that can be seen in both MI and panic attacks include dyspnoea, nausea, diaphoresis (sweating), palpitations and feeling light-headed [6, 9]. There are certain symptoms that are associated with panic attacks, but are not characteristic for MI: chills or heat sensations, derealisation and depersonalisation and trembling. However, back pain can be presented in case of MI as part of chest pain radiation, but is not characteristic for a panic attack. Another symptom that can be distinctive for MI, but is not associated with panic attacks, is fatigue [3]. Thus, there are similarities and differences in symptoms (Table 1).

Diagnosis

In patients presenting with acute chest pain, it is important to consider MI, pulmonary embolism, or aortic dissection [6]. ACS is more probable in patients with retrosternal pain for more than 20 minutes, with or without radiation, especially when accompanied by diaphoresis, nausea, or vomiting [6]. Chest pain described as sharp or stabbing in quality, affected by respiration or change of position, or reproducible by palpation of the area makes ACS less probable [5]. Because the diagnostic performance of chest pain characteristics is limited, an ECG should be performed on every patient presenting with acute prolonged chest pain [5].

MI

MI can be diagnosed based on clinical history, 12-lead ECG, and elevated biochemical markers, preferably cardiac troponin (Figure 1) [1]. In order to diagnose MI, a rise or fall of cardiac troponin values (with at least one value above the 99th percentile) should be present as well as at least one of the following criteria [1]:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes: ST-segment-T wave changes or new left bundle branch block;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs).

Panic attack and PD

According to the Diagnostic and Statistical Manual of Mental Disorders, a panic attack is accompanied by four or more symptoms (Table 1) and is considered to be a limited-symptom panic attack when less than four symptoms are present [9]. The psychiatric differential diagnosis should contain PD, generalised anxiety disorder, post-traumatic stress disorder, major depressive disorder, illness anxiety disorder and somatic symptom disorder [7]. Nevertheless, a profound evaluation of more acute causes of chest pain should not be excluded in the evaluation of underlying psychiatric disorders, as patients can have atypical presentations of MI [3].

A panic attack does not require an underlying diagnose in order to occur. However, if attacks are recurrent and unexpected, PD might be the underlying disorder [10]. In order to get diagnosed with PD, the patient's panic attacks cannot directly or physiologically result from substance use, medical conditions, or any other psychiatric disorder [9]. Additional

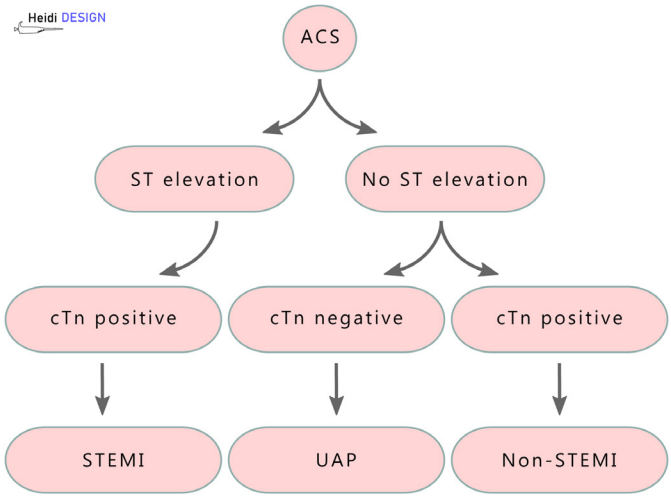

Figure 1: Interpretation of ST-segments and cardiac troponin (cTn)
Based on ST-segment characteristics and cTn levels, acute coronary syndromes (ACS) can be classified into unstable angina pectoris (UAP), non-ST elevation myocardial infarction (non-STEMI) and ST elevation myocardial infarction (STEMI).

criteria include that attacks must also be linked with persistent worry (for a minimal duration of 1 month) about (1) experiencing another attack or consequences of an attack, or (2) significant changes in behaviour in relation to the attack [2, 9].

Treatment
Patients with STEMI have to be treated with reperfusion therapy as soon as possible, preferably by means of percutaneous coronary intervention (PCI) within 90 minutes from the first medical contact [11]. PCI is a non-surgical procedure that utilises a catheter to open up cardiac blood vessels using a small device known as a stent without previous fibrinolytic treatment [11]. Current guidelines recommend performing PCI in patients presenting with symptoms of less than 12 hours duration or in patients presenting with cardiogenic shock or develop acute severe heart failure irrespective of time delay from onset of symptoms [11]. If PCI cannot be performed within the recommended timelines, fibrinolytic therapy should be given if it is not contraindicated [11].

For patients with non-STEMI or UAP, the approach to revascularisation differs from that in STEMI and is less urgent [12]. Once the diagnosis has been made, either an invasive or an ischaemia-guided strategy is applied [12]. For most patients, an invasive strategy (angiography or PCI) is favoured [12]. Urgent PCI is performed in patients whose condition is unstable. [3] Depending on the presence or absence of high-risk features, angiography is performed within 12 to 24 hours, or within 25 to 72 hours [12]. Fibrinolytic therapy may be harmful in non-STEMI patients and is therefore contraindicated [12]. Regardless of the strategy, both entail aggressive utility of medications such as anticoagulants, antiplatelet agents, beta-blockers, statins and possible use of angiotensin-converting enzyme inhibitors for appropriate patient populations [12].

After acute treatment in terms of medication and PCI, patients undergo long term pharmacotherapy to reduce morbidity and prevent complications. Pharmacological treatment usually includes aspirin, simvastatin, a beta-blocker, an angiotensin-converting enzyme inhibitor and a P2Y12 inhibitor, such as ticagrelor or clopidogrel [12].

PD therapy typically involves cognitive-behavioural therapy as a psychological intervention [2]. Cognitive-behavioural therapy is the first choice of treatment and can also be beneficial for people who experience panic attacks, but are not diagnosed with PD. The treatment can also be combined with pharmacotherapy to help reduce symptoms associated with panic attacks [2]. Selective serotonin reuptake inhibitors, a type of antidepressants, are the first choice of medication [2]. Other options include serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors and benzodiazepines [2]. In respect to negative adverse events, benzodiazepines are only prescribed when several antidepressants and behavioural therapy are proven not to be effective [2].

Conclusion

The diagnostic performance of chest pain characteristics is limited, but several discriminative differences between acute MI and panic attacks exist. Chest pain from MI and panic attack differs in character (typical anginal pain versus non-anginal pain) and duration (more than 20 minutes versus less than 10 minutes). Chest pain described as sharp or stabbing in quality, affected by respiration or change of position, or reproducible by palpation of the area makes ACS (and therefore MI) less probable.

Back pain as a part of chest pain radiation is not associated with panic attacks, whereas chills, heat sensations, derealisation and depersonalisation are not associated with MI. Fatigue is distinctive for MI but is not linked to panic attacks.

On the grounds that PD and ACS can co-occur and symptoms of both MI and panic attacks have an interindividual presentation, acute causes of chest pain should not be excluded in the evaluation of psychiatric disorders. Further diagnostic testing (for example an ECG) should be performed in every patient presenting with acute prolonged chest pain.

Acknowledgements

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1
A. Frontal lobe

The primary motor cortex is one of the principal brain areas involved in the motor function. It is located in the frontal lobe of the brain, next to the precentral gyrus. The function of the primary motor cortex is to generate neural impulses that control the execution of movement.

For further reading:
Moore, K.L., *et al. Chapter 8: Head* in Clinically Oriented Anatomy, Vol. 8e. (Wolters Kluwer, Philadelphia, 2018)

During the exam, 77% of the participants answered this question correctly.

Answer question 2
B. Medulla oblongata

Vital sensibility, consisting of the sensation of temperature and pain, crosses to the contralateral side immediately upon entering the central nervous system, therefore crossing at the spinal cord. Gnostic sensibility, encompassing touch and motor skills, crosses to the contralateral side much higher in the central nervous system, in the medulla oblongata.

For further reading:
Siegel, A. *et al.* Chapter 14: Somatosensory Systems in Essential Neuroscience, 4th edition. (Wolters Kluwer, Philadelphia , 2018)

During the exam, 46% of the participants answered this question correctly.

The exam questions can be found back on page 13 in this journal.

EDITOR'S CHOICE OF RECENT PAPERS FROM RADBOUDUMC RESEARCHERS

Jelmer Raaijmakers[1]

Summary

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

[1] Master Student Biomedical Sciences, Radboud university medical center, Nijmegen, the Netherlands.

Inhaled tigecycline is effective against *Mycobacterium abscessus in vitro* and *in vivo*

In collaboration with researchers at Colorado State University, Camron Pearce, with leading investigator Jakko van Ingen, PhD, published a new effective treatment of *Mycobacterium abscessus* (*M. abscessus*) tested both *in vitro* and *in vivo* in the Journal of antimicrobial chemotherapy (impact factor 4,940). *M. abscessus* is a bacterium that can cause severe, chronic, pulmonary infections in its host. The paper refers to *M. abscessus* as 'an antibiotic nightmare' as it is resistant to most classes of antibiotics, making treatment complex. Furthermore, the cure rate of this micro-organism is only 45%. This study explored whether *M. abscessus* pulmonary disease is treatable with 0.25, 1.25 and 2.5 mg doses of tigecycline in human macrophages inserted in mice for 28 days. Inhaled tigecycline proved to be highly effective against *M. abscessus* infection in GM-CSF (stimulating factor) knockout mice in a dose-dependent manner. Interestingly, the paper suggests that the effect of the inhaled tigecycline may have been underestimated in the mouse model experiment due to rapid degradation of the drug in aqueous environments. This inaccuracy means that the drug is expected to be even more effective than estimated in this study. From this study can be concluded that inhaled tigecycline could represent a viable treatment option for *M. abscessus* pulmonary disease, a disease where treatment outcomes are currently very poor. To proceed with this drug as a treatment for *M. abscessus* pulmonary disease infections, a stable and safe formulation is required to continue to further pharmacodynamic studies and, ultimately, clinical trials [2].

Catecholamines induce trained immunity in monocytes *in vitro* and *in vivo*

Catecholamine (e.g. noradrenaline and adrenaline) levels rise when an individual is subjected to stress, anxiety or pain. This explains the evolutionary function of catecholamines in the fight or flight response. Interestingly, high concentrations of catecholamines have also been found to be associated with a pro-inflammatory effect. Fellow researchers from the Radboudumc studied whether the pro-inflammatory effects of noradrenaline and adrenaline can in part be explained by the induction of immunological memory in innate immune cells, also known as 'trained' immunity. The rationale of this study is that it is known that exposure to high catecholamine levels is associated with inflammatory changes of myeloid cells (progenitor cell of various cells within the blood plasma) and atherosclerosis, but underlying mechanisms are only partly understood. Primary human monocytes were used, which are cells that are directly isolated from a biopsy and used for experiments. These monocytes were exposed to catecholamines, after which they differentiated into macrophages. Subsequently, these exposed macrophages were re-stimulated with lipopolysaccharide, an endotoxin. This re-stimulation showed that cells that were exposed to (nor)adrenaline had an increased tumour necrosis factor α (TNF-α) production. Furthermore, an *in vivo* study was performed on monocytes isolated from pheochromocytoma and paraganglioma patients, which are rare tumours that cause abnormal catecholamine levels in the blood. This study showed that catecholamines induce long-lasting pro-inflammatory changes in monocytes *in vitro* and *in vivo*. Research such as this helps us understand specific pathways that drive inflammatory changes which are characterised by catecholamine levels. In the end, the authors proposed that trained immunity underlies the increased cardiovascular event rate in certain patients. This paper was published in the Journal Circulation Research with an impact factor of 15,862 [3].

Assessment of placental disposition of infliximab and etanercept in women with autoimmune diseases and in the *ex vivo* perfused placenta

Various autoimmune diseases are known to affect women in their reproductive years, such as rheumatoid arthritis and inflammatory bowel disease. Infliximab and etanercept are TNF-α inhibitors that are used for the treatment of these autoimmune diseases in order to reduce inflammation. These therapies are increasingly applied to patients during pregnancy, even though little is known about their effect on the placenta and the foetus. Eliesen *et al.* from the Department of Pharmacology and Toxicology used both *in vivo* experiments and *ex vivo* placenta perfusion experiments to study the placental transfer of both these drugs. These experiments allowed greater insight into whether these drugs could pass the placental barrier and at which rate. This is important for the treatment of pregnant women since both the unborn child and the placenta could be negatively affected by the administration of the drug(s). In the placenta perfusion setup, the umbilical cord and a vein from a single cotyledon (functional unit foetal side of the placenta) are brought back into the circulation. With this technique, the drug concentration before and after passage through the placenta can be determined and the rate in which they pass the placenta can be calculated. In this study, they found that both drugs can be transferred into the cord blood and placenta, *in vivo* and *ex vivo*. However, tissue was exposed in a higher concentration to infliximab than etanercept, due to a higher transfer. In the future, it would be of interest to study the occurrence of placental TNF-α inhibition and what the possible consequences could be thereof. This research was published in the Journal of Clinical Pharmacology and Toxicology, a journal with an impact factor of 7,266 [4].

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RAMS

Word from the Board

Dear reader,

Thank you for reading the 16th edition of RAMS. With this academic year's final edition and also my last edition as a board member, we would like to look back on the previous editions. I hope that RAMS has enthused you to dig deeper into research. From digital diets and good microbes to post-orgasmic illness syndrome and the importance of sleep quality. RAMS covered it all!

While writing this, I'm enjoying my corona vacation in the confines of my balcony. In the past few months, I've assembled quite the collection of plants in my room. With a tiny bit of imagination, I can fantasise about laying at the beach, sipping a lovely cocktail while surrounded by tropical plants. Unfortunately, the sounds of my neighbours redecorating their room anew daily out of pure boredom awoke me from this daydream abruptly.

Once the academic year starts, I hope to find this edition of RAMS in paper at the faculty, where it belongs. Despite the unexpected setbacks, I am proud of what we have achieved. Together we hope that we can all return to our daily life as students, one step at a time.

Stay safe.

On behalf of the board of RAMS,

Davíd van Groeninghen,
Education Board Member of RAMS 2019-2020

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