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## Highlights

# What makes tics tick? Insights into Tourette syndrome

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### ABSTRACT

This issue of *Biomedical Journal* provides the reader with articles concerning the latest understanding of Tourette syndrome (TS), the relation to genetic predisposition, defects in the dopaminergic system, and related comorbidities which further complications like sleep disruption. Treatment approaches for TS, attention deficit hyperactivity disorder and developmental coordination disorder are discussed. The second section of this issue offers insights into inside out integrin activation and its link to T cell activation, demonstrates how polarity in immune cells allows adoption to specialized functions, and describes the endosomal signaling of internalized T cell receptors (TCRs). The link between mutations in TCR signaling and immunodeficiencies is elucidated, as well as the interactions of thymocyte-expressed molecule involved in selection in T cell development. Additionally, we learn about a potential biomarker for colorectal cancer, screening tools for determining frailty in older adults, surgical approaches in spinal metastases, the influence of autophagy on mating behavior, and the effect of nitrite administration on SNARE proteins associated with insulin secretion. Finally, parameters for surgery in breast cancer are discussed, as well as gender and age dependent pain perception in a lysosomal storage disease, and the use of laser meridian massage in opioid use disorder. Three letters complement this issue, one concerning neuroimaging in pediatric COVID-19 patients, and two discussing the role of cancer antigen-125 and renal impairment in ovarian cancer patients.

## Spotlight

Tourette Syndrome (TS) refers to a neurodevelopmental disorder characterized by motor and vocal tics that begin in childhood [1]. Tics are movements that are automatically made, often connected to an urge – a specific sensory feeling – preceding the tic. Patients report a temporary relief of the urge by executing the tic, however, since this can be

considered rewarding, repetition of the particular behavior may perpetuate the tic as a habit [2].

The syndrome has been named after Gilles de la Tourette, a French neurologist that is sad to have been an odd character, that worked at superhuman pace in terms of publishing, teaching and practicing clinical medicine [3].

TS affects up to 1% of the population. Children with TS may be accompanied by comorbidities such as attention deficit hyperactivity disorder (ADHD), which occurs in 55% of

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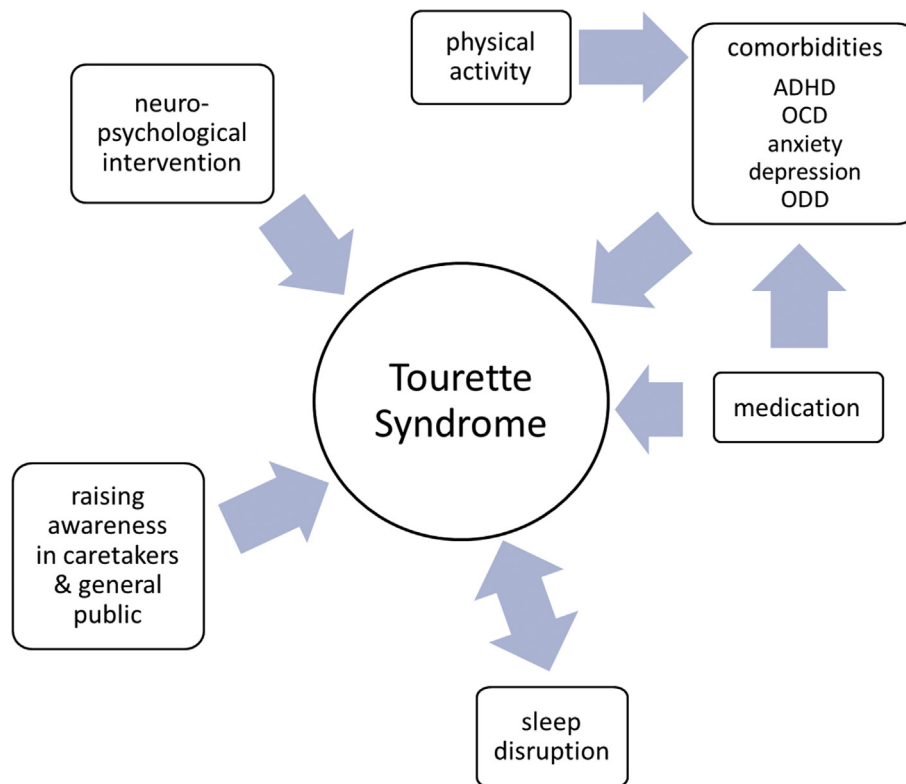


Fig. 1 Underlying factors like comorbidities (ADHD: attention deficit hyperactivity disorder, OCD: obsessive compulsive behavior, ODD: oppositional defiant disorder) and a choice of therapeutic strategies directly impacting Tourette Syndrome and thus indirectly affection sleep disruption in TS patients as proposed by Blaty and DeRosso [10].

children, obsessive-compulsive disorder (OCD), anxiety disorder or oppositional defiant disorder (ODD) [1,4].

TS has been popularly associated with coprolalia, the involuntary outburst of obscene words. Doctors mistakenly believed for years that a diagnosis of TS could not be confirmed unless coprolalia was present. However, coprolalia only occurs in a minority of TS patients.<sup>1</sup>

Pharmacological treatment is usually not indicated with the exception of severe cases, as children with TS respond well to comprehensive behavioral intervention. Tics often progressively decline during adolescence, and will resolve completely in one third of patients [1]. Available medication can reduce tics, however, they are not cures and treatments have potential side effects and risks. Pharmacological treatment of co-occurring conditions such as ADHD and OCD often improve the quality of life in patients with TS, and additionally result in a reduction of tics as well.<sup>2</sup>

Even though TS is often not life-threatening, tics and comorbidities affect a child's physical and mental health as well as its social interactions. Lee summarizes the current nursing care measures for youths with TS and symptom management. Individually tailored healthcare interventions and strategies to cope with interpersonal interactions are fundamental for the patient. Furthermore, raising awareness

in caretakers, peers and the general public are important to promote the social adjustment of youths with TS [5] [Fig. 1].

Although a genetic predisposition hypothesis is considered a key factor in the origins of TS, the currently most emphasized pathophysiologic hypothesis is based on a dopaminergic dysfunction in the cortico-striato-thalamo-cortical circuits [6]. Environmental factors like infection, autoimmunity or perinatal injury might also be contributing [1].

The development of human intelligence is hypothesized to be related to an expansion of human cognition through evolution of dopaminergic systems. The neuromodulatory molecule dopamine is critical for skills relating to human language and thought. Moreover, dopamine might have enabled early hominids to successfully chase-hunt in sub-Saharan Africa by counteracting hyperthermia during endurance activity. The entailing changes in physical activity and diet might have further contributed to an augmentation of dopamine in the central nervous system [7].

There are four major dopamine pathways in the body: the mesolimbic pathway mediating feelings of pleasure and reward. The mesocortical pathway involved in cognition, working memory and decision making. The nigrostriatal dopamine pathway that contains around 80% of dopamine in the brain and plays a role in stimulating purposeful movement. Finally, there is the tuberoinfundibular pathway that affects prolactin release.<sup>3</sup> The neurodevelopmental disorder

<sup>1</sup> <https://tourette.org/resource/understanding-coprolalia/>, last access 03/30/2022.

<sup>2</sup> <https://tourette.org/research-medical/pharmacology/>, last access 04/01/2022.

<sup>3</sup> <https://sanescoshealth.com/blog/dopamine-pathways/>, last access 03/29/2022.

TS is thought to be caused by an accelerated decrement of dopamine activity at the nigrostriatal pathway, and Nomura reviews the clinical characteristics, pathophysiology and treatment approaches. The author advocates choosing a tailored treatment strategy in order to target involved neuronal circuits and achieve individual patient goals. Next to psycho—behavioral support, proposed drugs include levodopa and aripiprazole in order to control tics without side effects. Also, dopamine blockers are recommended after the age of 10 [8] [Fig. 1].

Lin et al. have a closer look at the genetic factors that exert a vital role in the etiology of TS along with its comorbidities. The team recognizes that the genome-wide linkage studies performed so far only allow drawing limited conclusions. However, those studies strongly indicate that the genetic factors involved are far more complex than simple Mendelian inheritance. Candidate genes involve neuronal transmembrane genes as well as dopamine and serotonin system genes. Defects in the dopamine system in TS might be caused by a restriction fragment length polymorphism of the dopamine receptor D2 (DRD2) locus. However, also serotonergic receptors HTR1A and transporter SLC6A4 genes are linked to the condition [9].

Sleeping straight through from evening until morning became habitual to adult humans during the industrial era with the development of timekeeping and artificial light enabling people to stay up past sunset. However, a monophasic sleep pattern was largely preceded by biphasic sleep across the world. In Medieval Europe, Africa, South and Southeast Asia, Australia, South America and the Middle East accounts have been found for a first sleep usually before 10 pm. There would then be some time spent awake for socializing, for getting chores done like taking care of animals and for religious duties between 11 pm and 1 am. A second sleep phase would consequently follow, usually lasting until dawn.<sup>4,5</sup>

Blaty and DelRosso review sleep disorders in children with TS. Sleep would be disturbed due to various factors like for instance persistence of motor tics during both REM and NREM sleep, insomnia, parasomnias. However, also ADHD, which is often associated with TS as previously described, interferes with a healthy sleep pattern. Blaty and DelRosso do not find a significant association with sleep disordered breathing or circadian rhythm disorders in TS patients. They outline the importance of treating underlying TS as well as diagnosed comorbidities for the improvement of sleep related TS manifestations [10] [Fig. 1].

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## Also in this issue

### Editorial: Tourette Syndrome

Wang outlines the characteristics of patients with Tourette Syndrome (TS) and presents examples of how changes in lifestyle reduce the frequency and degree of the associated

tics and comorbidities. Wang furthermore introduces the articles of this special issue about current findings in TS [11].

### Reviews

#### *Small steps every day*

Developmental coordination disorder (DCD) describe difficulties with the organization, planning and execution of physical movement due to developmental rather than acquired origin [12]. The mainstream interest in the condition spiked massively with Ryan Sinclair, a character with dyspraxia in the TV series “Doctor Who” in 2018, and also when Daniel Radcliffe, the actor playing the main character in the Harry Potter movies, opened up about his dyspraxia.<sup>6</sup>

Smits-Engelsman and Verbecque present in their paper insights into current trends of DCD treatment and furthermore point out future alternative approaches to prevent secondary health implications in children with DCD. A critical factor consists in exploring ways of integrating everyday physical activities matching the child's interest and skill level to positively impact its physical fitness as well as its social-emotional well-being [13].

#### *Fire over water*

The neurodevelopmental impairment attention deficit hyperactivity disorder (ADHD) is often perceived to be a diagnosis of the 21st century. However, the father of modern medicine, Hippocrates, who lived around 400 BC, wrote about some patients unable to keep their focus on anything for long and reacting exceptionally quickly to things in their surroundings. Hippocrates attributed the issue to an overbalance of fire over water and recommended a specific diet including lots of water and physical exercise.<sup>7</sup>

Worldwide prevalence of ADHD in children and adolescent is around 7% [14] and as previously described, ADHD can also present as comorbidity in TS patients [10]. Pharmacological treatment of the disorder benefits from adjunctive therapy to foster cognitive function, executive function and motor abilities in pediatric patients. Chan et al. examine the effects of physical exercise in children with ADHD, highlighting the positive correlation between cognition and physical activity (PA) [15] [Fig. 1]. PA exerts beneficial neurocognitive effects, including reduction in stress, anxiety, and depression, furthermore improving executive and memory functions [14]. PA does not only improve the blood flow to the brain, an appropriate exercise intervention also augments sensorimotor skills, increases self-confidence and improves social interaction skills in children [15].

### Editorial: T cell activation

Kanellopoulos and Ojcius summarize the advances in understanding T lymphocyte signaling as presented in this special issue of *Biomedical Journal*. The five articles they go into focus

<sup>4</sup> <https://www.bbc.com/future/article/20220107-the-lost-mediterranean-habit-of-biphasic-sleep>, last access 03/28/2022.

<sup>5</sup> <https://www.sleepfoundation.org/how-sleep-works/biphasic-sleep>, last access 03/28/2022.

<sup>6</sup> <https://www.theunwritten.co.uk/2022/01/10/how-the-media-discusses-daniel-radcliffes-dyspraxia-is-outdated-and-damaging/>, last access 03/26/2022.

<sup>7</sup> <https://chadd.org/adhd-weekly/more-fire-than-water-a-short-history-of-adhd/>, last access 04/01/2022.

on the inside-out signaling linking integrin activation to T cell activation, constituents of the immunological synapse between lymphocyte and antigen-presenting cells (APCs), the surprising role of T cell receptor (TCR) signaling from endosomes, immune deficiencies originating in mutations of the T cell pathways, and the role of thymocyte-expressed molecule involved in selection (THEMIS) in T cell development and peripheral T cell function [52].

## Reviews

### Inside out

Integrins are heterodimeric transmembrane proteins and a major receptor class involved in adhesive events. They additionally transmit signals from inside cells to increase extracellular binding to ligands, a process known as integrin activation [16]. On top of that, this inside-out signaling is paramount in T cell activation. In T cells Rap1 regulates integrin activation through its downstream effector molecules RapL and Rap1-interacting adaptor molecule (RIAM), hence coupling TCR activation to integrin-mediated signaling. Sari-Ak et al. discuss the structural and molecular properties of RIAM and recent findings regarding the Rap1/RIAM module in hematopoietic cells. Rap1/RIAM are involved in myeloid cell differentiation. Next to RIAM contributing to integrin activation, Rap1/RIAM was reported to fine-tune T cell signaling events. Furthermore, RIAM's involvement is crucial in phagocytosis. It is also linked with actin polymerization and cytoskeletal remodeling [17].

### Specialized and versatile immune cells

About 3.5 billion years ago the first known single-cell organisms appeared on Earth, approximately a billion years after the formation of Earth. The first multicellular organisms then emerged around 600 million years ago.<sup>8</sup> Multicellular organisms can arise through cell aggregation or division [18],<sup>9</sup> and the evolution of multicellular life drastically reshaped the ecology of our planet. It seems that the first primitive multicellular organisms experienced both multicellular and unicellular states<sup>10</sup> until a “ratcheting” mechanism facilitated the loss of evolutionary autonomy, thus fostering mutual reliance [19]. Although multicellularity comprises trade-offs like sharing resources, there are advantages in terms of fitness, survival, and division of labor [20,21]. Cell-autonomous polarity has been evolutionary conserved from unicellular eukaryotes to Metazoans. It was vitally important in the advancement of individuality [21].

Immune cells notably possess particular versatility by rapidly polarizing and assuming different shapes to adopt specialized behaviors and functions. Mastrogiovanni et al. performed a review on how evolutionary conserved cell polarity regulators control the processes involved in T lymphocyte physiology including cell migration through

reorganization of the actin cytoskeleton, and antigen-induced responses. Involved molecules are likely Rho family GTPases, although polarity regulators endeavor numerous protein–protein interactions. Hence, a much wider mode of interplay is suggested [22].

### Is there anybody out there

Endocytosis facilitates a range of cellular processes in eukaryotes, including compartmentalization of chemistry within cells and internalization of extracellular molecules. Clathrin-mediated endocytosis is well-described and universal. Clathrin independent forms are poorly understood and limited to specific cell types or lineage states. Endocytosis in T cells is *inter alia* regulating plasma membrane immune receptors and signaling, including internalization and recycling of T cell antigen receptors (TCRs) [23].

Evnouchidou et al. review how the molecular mechanism of endosomal recycling and signaling platforms contribute to T cell activation. Experimental data indicates that after activation, the internalized TCR can still signal from endosomes, although the endosomal source of TCR ligands remains unclear. The endosomal signaling might serve in amplifying and diversifying TCR signaling, as the signal coming from the plasma membrane can thus be transmitted over longer distances. Additionally, it allows for a spatial separation of phosphorylated signaling adaptors from inactivating phosphatases [24].

### Specialized co-molecules in T cell response

The T cell receptor (TCR) mediates recognition of peptide fragments that are bound to major histocompatibility complex (MHC) on antigen-presenting cells (APC). The receptor consists of a heterodimer of two chains and is non-covalently associated with CD3 dimers. The TCR is highly sensitive and recognizes a few copies of a specific peptide in a number of as many as 100,000 MHC-bound peptides displayed on an APC [25].

The TCR also plays a role in T cell development, activation and immune tolerance. It is important in thymocyte selection to ensure that only those develop into mature T cells that are self-tolerant, thus eliminating the self-reactive T cells. TCR signaling and co-signaling involves next to the TCR-CD3 complex protein tyrosine kinases and phosphatases, adaptor proteins, co-receptors, second messenger  $Ca^{2+}$ , MAPK pathway and more [26].

Latour outlines the relation between primary immunodeficiencies and defects in development and activation of T lymphocytes. Mutations in TCR signaling components are involved in causing immune dysregulation manifestations such as autoimmunity and inflammation. These defects are especially associated with susceptibility to pathogens like Epstein–Barr virus or Human Papilloma Virus which suggests a specialization of co-stimulatory molecules taking part in T cell responses to specific pathogens [27].

### Thymocyte-expressed molecule involved in selection

The Hellenic goddess Themis is the equivalent to the Roman goddess Justitia, and stands for law, order and justice. Justice is typically represented with scales weighing a person's soul against the feather of truth. She furthermore carries a sword

<sup>8</sup> <https://astrobiology.nasa.gov/news/how-did-multicellular-life-evolve/>, last access 03/25/2022.

<sup>9</sup> <https://www.nature.com/scitable/topicpage/volvox-chlamydomonas-and-the-evolution-of-multicellularity-14433403>, last access 03/25/2022.

<sup>10</sup> <https://astrobiology.nasa.gov/news/how-did-multicellular-life-evolve/>, last access 03/25/2022.

to depict justice as swift and final. Lastly, she is usually shown to be blindfolded, as she does not bother with status, wealth or emotional impressions of the accused to be swayed in her impartial judgement.<sup>11</sup>

THEMIS also stands for thymocyte-expressed molecule involved in selection. Mélique, Yang and Lesourne present an overview of the current understanding of the structure and molecular function of THEMIS during T cell development, where it interacts with tyrosine phosphatases SHP-1 and SHP-2. The research team highlights growth factor receptor-bound protein 2 (GRB2) as the most important binding partner of THEMIS in both thymocytes and peripheral T cells. GRB2 facilitates THEMIS interaction with SHP-1, and furthermore prevents proteasome-mediated degradation of THEMIS [28].

### Original articles

#### *A missense mutation as potential biomarker*

Chiang et al. performed an observational study comparing tumor and adjacent normal tissue samples from Taiwanese patients with stage III colorectal cancer (CRC). As a rise in incidences has been observed, the team sees an urgent need for the discovery of effective biomarkers for diagnosis and prognosis of CRC. Chiang et al. profiled DNA, mRNA and miRNA sequences of the tissue pair samples and found a correlation between adenomatous polyposis coli gene mutation status and outcome in CRC patients [29]. The tumor suppressor gene had been first discovered in 1986 and absence of adenomatous polyposis coli indicates inadequate emigration of colon mucous cells and consequent accumulation resulting in polyp formation, which determines a stage in carcinogenicity. Adenomatous polyposis coli mutation causes the inherited, autosomal-dominant cancer predisposition familial adenomatous polyposis. A high-risk religious-ethnic group are Ashkenazi Jews with a prevalence of 10% of a specific adenomatous polyposis coli missense mutation amongst them [30].

Chiang and team discovered that overall survival rate and disease-free survival of Taiwanese patients with mutated adenomatous polyposis coli was higher than in those with wild type adenomatous polyposis coli [29].

#### *Yabba-Dabba-Doo*

Elderly individuals have often been considered asexual, especially when living in institutional care. However, people in nursing home care report having intimate needs and sexual desires in equal proportions to non-institutionalized older adults. Elders who wish to express their sexuality in long-term care facilities often face specific obstacles like limited privacy, health concerns, negative staff attitude and potential legal implications for the facility [31]. Lack of educational support in the facility can cause further complications like the increase of sexually transmitted infections in inhabitants [32,33]. Care facilities are confronted with tackling this taboo<sup>12</sup> as sexual wellbeing is a key element to overall health and quality of life. Furthermore, paying

attention to sexual health when assessing frailty-related deficits in seniors allows a more holistic evaluation of late life health [34]. Sexual activity also appears to exert an effect against frailty of the elderly [35].

Different standards are used to detect frailty in elderly patients. Chen et al. compared the diagnostic performance of two screening tools to identify frailty risk in older patients with cancer. The team concludes a routine screening essential in elderly patients and sees a better fit of the Geriatric 8 (G8) in opposition to the Flemish version of the Triage Risk Screening Tool (fTRST) for Taiwanese cancer patients [36].

#### *Choice of surgical approach in spinal metastases*

Spinal metastases are the most common tumors of the spine. Metastasis is most frequently found in the thoracic region, followed by the lumbar region, and least likely to be found in the cervical region. While all tumors can seed to the spine, the following primary malignancies tend to metastasize to the spine early in the disease process: breast (21%), lung (19%), prostate (7.5%), renal (5%), gastrointestinal (4.5%) and thyroid (2.5%) [37].

In a retrospective study, Liao et al. investigated the outcome in patients with metastatic lesions within the thoracic spine who underwent surgery. The team was especially interested in evaluating survival time, neurologic status and complications during surgery or in hospital between patients undergoing either anterior thoracotomy or a posterior approach. Liao et al. concluded a preference for the posterior approach given the lower surgical complication rate and fewer days needed post-surgery in intensive care [38].

#### *How autophagy influences mating behavior*

Autophagy has been evolutionary highly conserved. It delivers cytoplasmic material to the lysosome for degradation to provide raw material for instance for the survival of cells under stress. Autophagy also plays a pivotal role in reproductive processes in terms of resource allocation in different taxonomic categories [39].

In humans, dysregulation of autophagic flux is associated with neurodegenerative diseases, cancer, infectious diseases and metabolic diseases. Fontana et al. performed a study in zebrafish to elucidate recent findings, highlighting the central role of autophagy in reproduction. The team used an *egp5* knockout zebrafish model. EGP5 is a metazoan specific autophagy-related protein. The team observed a high variability in male zebrafish phenotype expression as well as an effect on their reproductive behavior, which might be linked to a lower overall reproductive success in the knockout group [40].

#### *Nitrite and insulin in type 2 diabetes*

Since insulin signaling is essential for nitric oxide (NO) production, loss of bioavailable NO impacts the development of insulin resistance. In a previous study it has been shown that providing dietary nitrite in mice improved insulin-mediated signaling [41].

Ghasemi and colleagues performed a study in type 2 diabetic (T2D) rats to demonstrate the influence of nitrite on insulin secretion [42]. As insulin is stored in large granules, and biphasically exocytosed by glucose stimulation in pancreatic

<sup>11</sup> <https://www.theclassroom.com/symbolism-of-lady-justice-12080961.html>, last access 04/08/2022.

<sup>12</sup> <https://www.agingcare.com/articles/seniors-and-sex-elder-care-facilities-tackle-taboos-156112.htm>, last access 04/02/2022.

$\beta$ -cells, molecules such as SNARE proteins and  $\text{Ca}^{2+}$  ions are involved in insulin exocytosis [43]. Ghasemi et al. show that the stimulatory effect of nitrite on insulin secretion is at least partially due to increased gene expression of molecules taking part in glucose sensing, calcium sensing and exocytosis of insulin vesicles, as well as increased expression of insulin genes. The team thus provides the first study reporting stimulatory effect of long-term *in vivo* nitrite administration on SNAREs associated with insulin secretion from isolated pancreatic islets of T2D rats [42].

#### A sentinel approach

Sentinel species are animals or plants that are highly sensitive to environmental factors that are also dangerous to humans. Canaries for example were used in coal mines to detect carbon monoxide levels before the latter would critically affect the workforce. In Japan in the 1950s, the “dancing cat fever” raised awareness to the poisoning of wastewater with methylmercury from a local chemical factory. Shortly before humans began to react, the cats were observed to be unable to walk straight due to consuming mercury-contaminated fish from the polluted waters.<sup>13</sup> Lastly, when assessing marine ecosystems, exposure to pollutants can be detected as it is linked to an increased prevalence of cancer in exposed marine mammal populations with long lifespans [44].

Sentinel lymph node biopsy (SLNB) is used as standard axillary staging approach for early breast cancer. In their article Liu et al. elucidate parameters to facilitate a surgeon's decision for the removal of hot, radioactively labeled and non-hot, unlabeled nodes. The retrospective study revealed that suspicious non-hot nodes larger than 2.5 cm should be included for a precision therapy [45].

#### A lysosomal disorder and gender-dependent pain perception

Lysosomal storage diseases comprise metabolic disorders caused by deficient lysosomal function. The current understanding of lysosomes changed from the original classification as organelles exclusively involved in catabolic pathways to highly dynamic elements taking part in multiple cellular functions. This refined vision opened new insights into the pathophysiology of lysosomal disorders where substrate accumulation triggers complex cascades and disease pathology such as aberrant vesicle trafficking, impairment of autophagy or dysregulation of signaling pathways [46].

Liao and team explored the relationship between small fiber neuropathy, age, sex, and pain intensity in the context of Fabry disease [47]. Fabry disease is an X-linked lysosomal storage disease characterized by a lack of alpha-galactosidase activity resulting in the accumulation of globotriaosylceramide in the cells of various systems, finally leading to multi-systemic effects [48].

The research team evaluated C-fiber function through recording withdrawal latency to painful heat stimulus. They propose a mechanism by which globotriaosylceramide or globotriaosylsphingosine is gradually deposited into small nerve bundles with increasing age, producing neuropathic pain in young male Fabry patients. Female Fabry patients on

the contrary present less and variable small fiber damage, pain intensity and clinical signs [47].

#### Laser massage against cravings for Miss Emma, Captain Cody, and Tango and Cash

Opioids include compounds extracted from poppy seeds as well as semisynthetic and synthetic compounds with similar properties, targeting the opioid receptors in the brain. The prolonged medical use for instance for treatment of pain with morphine, fentanyl and tramadol but also non-medical use can lead to various health issues and opioid dependence. 70% of deaths worldwide attributed to drug use are related to opioids. Accidental overdoses have been increasing recently due to the appearance of highly potent opioids on illicit drug markets, and drug dealers lacing their products such as heroin with fentanyl to increase the potency. In the U.S. the number of people dying from opioid-related overdose has increased by 120% between 2010 and 2018.<sup>14</sup>

Opioid use disorder (OUD) is typically a chronic, relapsing illness with increased rates of morbidity and mortality. In OUD patients who have achieved abstinence, the main focus lies on preventing relapse. Long-term maintenance treatment makes use of an opioid antagonist like methadone, the opioid antagonist naltrexone or non-medication based treatment.<sup>15</sup>

As the opioid related overdose constitutes a major challenge on a global level, Hu et al. set out to investigate the effects of adjuvant laser meridian massage (LMM) in male OUD patients receiving methadone maintenance treatment. The team observes a significant decrease in heroin use in the experimental group while the control group exhibits a significant increase in heroin craving [49].

#### Letters

##### Neuroimaging in children with COVID-19

Finsterer replies to the review by Wong and Toh concerning the neuroimaging findings in pediatric COVID-19 patients [50], offering a row of supplemental neuroimaging abnormalities in that patient group that Finsterer considers not having been addressed in the review. The author encourages further discussion to complete the presentation by Wong et al. [51].

#### Conflicts of interest

The author declares no conflicts of interest.

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<sup>14</sup> <https://www.who.int/news-room/fact-sheets/detail/opioid-overdose>, last access 04/07/2022.

<sup>15</sup> <https://www.uptodate.com/contents/opioid-use-disorder-epidemiology-pharmacology-clinical-manifestations-course-screening-assessment-and-diagnosis>, last access 04/07/2022.

<sup>13</sup> <https://cen.acs.org/articles/95/i46/meet-the-sentinels.html>, last access 04/02/2022.

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